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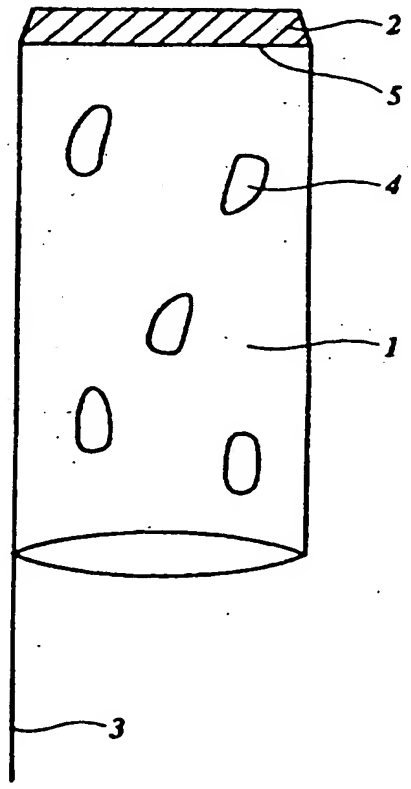
(54) Title: DEVICE FOR ENHANCED DELIVERY OF BIOLOGICALLY ACTIVE SUBSTANCES AND COMPOUNDS IN AN ORGANISM

(57) Abstract

A device to enhance the delivery of a drug or other substance of interest into a selected organ or tissue, comprising special electrodes, one of the electrodes carrying a container with the selected drug or other substance of interest, said electrodes being capable of being positioned at preselected locations of said organ or tissue, wherein the electrodes are all connected with a selected energy source which generates and maintains an energy field before and during the enhanced delivery of said substance, under the influence of which delivery is accomplished in a direction from the active to the passive electrode and into said organ or tissue. The energy source may be selected from suitable sources providing an electric field, a magnetic field, ultrasonic waves, high energy waves like laser beams, or a combination thereof. Further a method for the enhanced delivery of said drug or other substance of interest to an internal organ or target tissue of an organism, for example the brain, bypassing the blood-brain barrier, is disclosed.



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Device for enhanced delivery of biologically active substances and compounds in an organism.

1. INTRODUCTION

Most of the efforts currently under way to discover new therapeutic drugs for disorders of the central nervous system (CNS) will also face the problem of delivering them to the brain without impairing the activity or integrity of such substances or compounds, while minimizing systemic adverse effects. And that means finding a way around - or through - the blood brain barrier (BBB), a physiological barrier between bloodstream and brain.

A National Institutes of Mental Health (NIMH) study shows that, in the United States, one out of three individuals suffers from a CNS disorder at some time in life. Approximately two million in the same country have suffered a stroke, which is the third leading cause of death in the United States [17, 18].

2. IONTOPHORESIS

After the discovery of the electrical nature of nerve impulse by Galvani in 1791, attention focused on the possibility of using electricity as a mode of drug delivery. Galvani provided a major stimulus for Volta to discover a source of constant current electricity, the voltaic pile or battery, and new research on the effects of direct current (DC) on animal tissues broadened the scientific basis for the entire subject of electrophysiology. It had long been known that medicines could be introduced into the human body by way of the skin. The skin has a selective permeability to lipophilic (lipid soluble) substances and acts as a barrier to hydrophilic (water soluble) substances. In 1747, Veratti suggested that hydrophilic drugs might be introduced to the subcutaneous tissue through human skin by the application of a direct current [5]. This mode has become known as iontophoresis (meaning ion transfer).

In Table 1 we present several examples of drugs introduced through the skin by iontophoresis for some conditions.

	Drug	Condition
1.	Acetic acid	Myositis ossificans
2.	Aspirin	Rheumatic diseases
3.	Dexamethasone and lidocaine	Tendinitis, bursitis, rheumatoid arthritis
4.	Diclofenac sodium	Scapula-humeral periarthritis, elbow epicondylitis
5.	Iodine	Fibrosis, adhesions, scar tissue, trigger finger
6.	Lidocaine	Local anesthesia
7.	Lithium	Couty arthritis
8.	Morphine	Postoperative analgesia
9.	Pilocarpine	Sweat test (cystic fibrosis)
10.	Pirprophene	Rheumatic diseases
11.	Potassium citrate	Rheumatoid arthritis
12.	Potassium iodide	scar tissue
13.	Silver	Chronic osteomyelitis
14.	Salicylate	Plantar warts, scar tissue
15.	Sodium fluoride	Tooth hypersensitivity

Table 1: Drugs introduced by iontophoresis for corresponding conditions.

This is only a small part of different drugs or biologically active substances that can be introduced by iontophoresis. The skin is a multicomponent, multifunctional organ that is involved in the body's interactions with, and adaptation to, the environment. It is composed of the dermis and epidermis. The thickness of the dermis varies from 1 mm on the scalp to 4 mm on the back. Blood vessels, lymphatic vessels, nerve endings, hair follicles, sebaceous glands, and sweat glands are all located in the dermis. The epidermis ranges from 0.075 to 0.15 mm in thickness, except on the palm and the sole where it can be up to 0.6 mm thick. Many lipophilic drugs, such as scopolamine for motion sickness, clonidine for hypertension, and nitroglycerine for the

treatment of angina pectoris, can be readily delivered through human skin. With these drugs, the concentration gradient between the drug-loaded reservoir and the body is sufficient enough to deliver the drug through the skin at therapeutic dosage rates. However, this is not the case for hydrophilic drugs [20].

Because topical application fails to deliver therapeutic dosages of hydrophilic drugs, traditional methods, such as oral or parenteral systemic drug administration, have been favoured. However, these methods have several disadvantages.

First, systemic administration may lead to massive inactivation of a drug as a result of the enzymatic action of the liver. Also, oral administration may give rise to incomplete or erratic absorption due to factors like food interaction, inactivation in the gastro-intestinal tract, disease status, and concomitant medication. Furthermore, oral drug administration may give rise to fluctuations in the concentration of a drug in the systemic circulation. This may in turn result in toxic or subtherapeutic blood levels of the drug.

These problems have been and still are the subject of extensive research and can only partly be dealt with in most cases using different methods including oral administration of prodrugs and controlled release dosage forms. However, these problems may also be avoided by the use of iontophoresis. Using electric current as an external driving force, hydrophilic drugs can be readily introduced through the epidermal level.

Various types of drugs are potential candidates for iontophoresis. Hydrophilic drugs with relatively low molecular weight are the most suitable for the procedure, although the delivery of some large peptides and hormones by this technique has also proven to be successful [5, 3, 6].

Direct current, or galvanic current, is the current of choice for iontophoresis. Direct current allows the maximum ion transfer per unit of applied current, because its course is uninterrupted [7].

According to Ohm's law:

$$V = IR,$$

where V is voltage, I is current, and R is resistance, the voltage generated within the system is therefore dependent on the resistance of the skin or other tissue during the treatment.

It has been suggested by many investigators that penetration of hydrophilic substances occurs mainly by way of sweat ducts, sebaceous glands, and hair follicles and imperfection of the skin (The Shunt Pathway theory [3, 10, 23, 4]).

According to the flip-flop gate mechanism, it has been suggested that permeability of skin may be altered as a result of the application of an electric potential across the skin [5, 6]. Jung et al. in 1983 found that the only structural requirement for pore formation was the presence of alpha-helical polypeptides [12]. When an electric potential is applied across a physiological membrane, a voltage-dependent "flip-flop" of the helices occurs. The skin permeability can be enhanced by the formation of "artificial shunts" by the use of direct current as applied during iontophoresis [5, 6].

The following factors affect iontophoretic skin permeation:

- molecular weight,
- current density,
- skin impedance,
- ion conductivity,
- pH of the drug solution,
- ion valence,
- duration of iontophoresis,
- concentration of the drug ion in the solution.

In optimal conditions, an organism receives only 10% of the substance on the electrode applied to the skin. In fact, an organism may receive from 1 to 10% of the substance.

Therapeutically, a current density of less than 1 mA per square inch of electrode surface is recommended [7].

According to Faraday's First Law of Electrolysis, which states that the mass of a substance liberated at (or dissolved from) an electrode during electrolysis is directly proportional to the quantity of electrolyte.

An electrolyte can be defined as a substance that conducts electric current as a result of dissociation into positively and negatively charged particles called ions, which migrate toward and ordinarily are discharged at the negative and positive electrodes (cathode and anode respectively), of an electric circuit. The most familiar electrolytes are acids, bases, and salts, which ionize when dissolved in such polar solvents as water or alcohol. An essential requirement for solvents to be used is that they conduct electric current and have to possess an electric dipole.

Polar solvents consist of strong dipolar molecules having hydrogen bonding. Water is a very unique polar solvent in that it also has a high dielectric constant, which indicates the effect that a substance has, when it acts as a medium, on the ease with which two oppositely charged ions may be separated. The higher the dielectric constant of a medium, the easier it is to separate two oppositely charged species in that medium, which is an essential requirement for the existence of ionized molecules that may be moved by an electric current, as with iontophoresis.

Table 2 shows some useful polar solvents with their dielectric constants. The values listed are relative to a vacuum which by definition has dielectric constant of unity.

Solvent	Dielectric constant (ε) (at 20° C)
Water	80
Glycerin	46
Ethylene glycol	41
Methyl alcohol	33
Ethyl alcohol	25
n-propyl alcohol	22

The degree of dissolution and subsequent ionization can be improved and regulated by means of the addition of

suitable electrolytes forming buffer systems in the selected polar solvent or mixtures thereof.

Seddiqui et al [22] found that during passive absorption the penetration rate was greatest at the higher pH levels (9.4 and 11.7), where lidocaine is mainly non ionized. On the other hand, lidocaine is mainly in the ionized form at pH 3.4 and 5.2.

During iontophoresis, drugs do not penetrate to a big depth. After applying a current of 5 mA to the right side and 0 mA to the left side for 20 minutes, radiolabeled Dexamethasone was detected to a maximal depth of 1.7 cm in the right side, which was the location of the hip joint capsule of the monkey (Glass et al [9]).

For electrophoresis, not only direct (galvanic) current can be used, but other different impulse currents as well of both direct polarity and alternating polarity in a rectified regime (diadinamic, sinusoidal, fluctuating, etc.).

It is possible to use or to combine different types of energy. For example, we can combine iontophoresis with ultrasound, magnetic field, temperature-increase, etc.

When choosing a polarity, it is necessary to take into account that ions of all the metals, of local anaesethic drugs, of most alkaloids, and of antibiotics have all a positive charge. Therefore, it must be introduced from an anode. On the other hand, ions of all the metalloids and of acid radicals have all a negative charge, and must be introduced from a cathode. There have been a series of interesting results proving a successful introduction of drugs and other chemical substances into animals brain by means of iontophoresis [15, 1].

3. PHARMACOKINETICS

3.1. Physicochemical factors in transfer of drugs across membranes.

The absorption, distribution, biotransformation, and excretion of a drug all involve its passage across cell membranes. Important characteristics of a drug are its molecular size and shape, degree of ionization, and relative lipid solubility of its ionized and nonionized forms.

Passive Processes

Drugs cross membranes by either passive processes or by mechanisms involving the participation of components of the membrane. Both non-polar lipid-soluble compounds and polar water-soluble substances that retain sufficient lipid solubility can cross the lipid portion of the membrane by passive diffusion. Such transfer is directly proportional to the concentration gradient across the membrane. The greater the partition coefficient, the higher is the concentration of drug in the membrane and the faster is its diffusion. The bulk flow of water carries with it any water-soluble molecule that is small enough to pass through the channels. Filtration is a common mechanism for transfer of many small, water-soluble, polar and nonpolar substances.

Capillary endothelial cells have large channels (40Å), and molecules as large as albumin may pass to a limited extent from the plasma to the extracellular fluid. In contrast, the channels in the intestinal epithelium and most cell membranes are about 4Å in diameter and permit passage only of water, urea, and other small, water-soluble molecules. Substances generally do not pass through channels in cell membranes if their molecular mass is greater than 100 to 200. Most inorganic ions are sufficiently small to penetrate the channels in membranes, but their concentration gradient across the cell membrane is generally determined by the transmembrane potential.

Weak Electrolytes and Influence of pH.

Most drugs are weak acids or bases and are present in solution as both the nonionized and ionized species. The nonionized portion is usually lipid soluble and can readily diffuse across the cell membrane. In contrast, the ionized fraction is often unable to penetrate the lipoid membrane because of its low lipid solubility, or to pass the membrane channels because of its size. If the ionized portion of a weak electrolyte can pass through the channels, or through the membrane, it will distribute according to the transmembrane potential in the same manner as an inorganic ion.

Carrier-mediated active membrane transport.

Passive processes do not explain the passage of all drugs across cell membranes. Active transport is responsible for the rapid transfer of many organic acids and bases across the renal tubule, choroid plexus, and hepatic cells. The transported substance is transferred against an electrochemical gradient.

Transcellular fluxes are formed by the active transport of Na^+ across epithelial cells. Proteins and other macromolecules slowly cross epithelial cells by pinocytosis, a form of vesicular transport.

3.2 ABSORPTION OF DRUGS

It is of practical importance to know the manner in which drugs are absorbed. The rate of absorption influences the time course of drug effect, and it is an important factor in determining drug dosage. In addition, choice of the route by which a drug is administered is often influenced by considerations of drug absorption.

Factors that modify absorption.

Absorption from all sites of administration is dependent upon drug solubility. Drugs given in aqueous solution are more rapidly absorbed than those given in oily solution, suspension, or solid form. For those given in solid form, the rate of dissolution may be the limiting factor in their absorption. Local conditions at the site of absorption alter solubility. Thus, at the low pH of the gastric juice, many acidic drugs are absorbed slowly because they precipitate in the fluid of the stomach, and dissolution occurs very slowly. Highly insoluble substances may not be absorbed from the alimentary tract at all. The concentration of a drug influences its rate of absorption.

Drugs ingested or injected in solutions of high concentration are absorbed more rapidly than are drugs in solutions of low concentration. The circulation to the site of absorption also affects drug absorption. Increased blood flow, brought about by massage or local application of heat, enhances absorption of a drug. The area of the absorbing surface to which a drug is exposed is one of the more important determinants of the rate of drug absorption.

Enteral (Oral) vs. Parenteral Administration.

Often there is a choice of the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Oral ingestion is the most ancient method of drug administration. Disadvantages to the oral route include emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric pH, and formation with food of complexes that cannot be absorbed. Drugs absorbed from the gastrointestinal tract may be extensively metabolized by the liver before they gain access to the general circulation. The parenteral injection of drugs has certain distinct advantages over oral administration. In some instances, parenteral administration is essential for the drug to be absorbed in active form. Absorption is usually more rapid and more predictable than when a drug is given by mouth. In emergency therapy, parenteral administration is particularly serviceable. If a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may become a necessity. The injection of drugs also has its disadvantages. Strict asepsis must be maintained to avoid infection, an intravascular injection may occur when it is not intended, pain may accompany the injection, and it is often difficult for a patient to perform the injection himself if self-medication is a necessary procedure. Parenteral therapy is also more expensive and less safe than oral medication.

Oral Ingestion.

The rate of absorption of drugs from the gastrointestinal tract is generally proportional to the lipid solubility of the compound in question. If the drug is a weak acid or base, its nonionized form is more lipid soluble, and the pH within the gastrointestinal tract becomes a 'major determinant. Alcohol, a lipid-soluble nonelectrolyte, is rapidly absorbed into the blood stream by diffusion across the gastric and intestinal mucosae. Quaternary ammonium compounds and other completely ionized, lipid-insoluble drugs are very slowly absorbed. Other drugs are poorly absorbed because even their nonionic forms are lipid insoluble.

Weak bases, such as quinidine and ephedrine, which are predominantly ionized at the pH of the gastric juice, are poorly absorbed through the gastric mucosa and are absorbed mainly through the intestinal mucosa. Weak acids, such as salicylates and barbiturates, which are predominantly nonionized in the acid gastric contents, are more readily absorbed from the stomach.

If the gastric contents are made alkaline, acidic compounds become more ionized and may be more slowly absorbed. However, gastric pH also influences solubility of the drug and dissolution of solid dosage forms. In addition, the net effect of change in gastric pH may be relatively minor, since absorption of most drugs occurs primarily from the intestine because of its greater surface area. For the same reason, the absorption of most drugs is delayed or reduced if gastric emptying is retarded.

Absorption from the alimentary tract may be decreased if the ingested drug is unstable in gastrointestinal fluid or if it is bound to food or other gastrointestinal contents. Simultaneous ingestion of food also delays absorption by delaying gastric emptying. Drugs that are destroyed by gastric juice or that cause gastric irritation are sometimes administered in dosage forms with a coating that prevents dissolution in the gastric contents. However, some enteric-coated preparations of a drug may also resist dissolution in the intestine, and very little of the drug may be absorbed.

The dissolution rate of some preparations in gastrointestinal f luid may be quite irregular because of variations in gastrointestinal pH, gastric emptying, intestinal motility and other physiological factors that influence drug absorption. Moreover, slow absorption from the gastrointestinal tract is often incomplete and erratic. Drugs given for a brief therapeutic effect should not be in the timed-release form. Conversely, timed-release preparations are not needed for drugs with an inherent long duration of effect. Also, timed-release preparations of some drugs might not be safe.

Sublingual Administration

Absorption from the oral mucosa is rapid, and higher concentration of the drug in the blood may be achieved by this route than by absorption lower in the alimentary tract. This can result because metabolism of drugs as a result of passage through the liver is minimized, and because the drug is not subjected to possible destruction by the gastrointestinal secretions or to formation of complexes with foods. However, substances that are distasteful or that are irritating should not be given by this route. The sublingual route of administration permits rapid absorption of nitroglycerin and other drugs. It is a convenient method when the drug is suitable for such administration.

Rectal Administration

The rectal route is often useful when oral ingestion is precluded by vomiting or when the patient is unconscious. In addition, the absorbed drug does not pass through the liver before entry into the systemic circulation. However, rectal absorption is often irregular and incomplete, and many drugs cause irritation of the rectal mucosa. The major routes of parenteral administration are intravenous, subcutaneous, and intramuscular. Absorption of lipid-soluble drugs from subcutaneous and intramuscular sites also occurs by simple diffusion through the capillary membranes into the blood.

Lipid-insoluble drugs are absorbed by penetration through the relatively large aqueous channels in the endothelial membrane; larger molecules, such as proteins, gain access to the circulation by way of lymphatic channels, Some large molecules and microcrystalline substances are absorbed from these sites by phagocytosis. Certain irritating and hypertonic solutions can be given only in this manner. Repeated intravenous injections are dependent upon the patency of veins.

Drugs in an oily vehicle should not be given by this route. Injection at a subcutaneous site can be used only for drugs that are not irritating to tissue. Drugs in aqueous solution are rapidly absorbed after intramuscular injection. Irritating substances that cannot be injected subcutaneously may often be given intramuscularly. Occasionally a drug is injected directly in an artery to localize its effect in a

particular tissue or organ. Antineoplastic agents are sometimes given in this manner for the treatment of localized tumours.

Vaginal administration

The vaginal route is sometimes useful when other routes are disadvantageous for some reason.

Intrathecal administration

The blood-brain barrier and the blood-cerebrospinal fluid barrier often preclude or slow the entrance of drugs into the central nervous system (CNS). Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anaesthesia or acute CNS infections, drugs are sometimes injected directly into the spinal subarachnoid space.

Intraperitoneal administration

The peritoneal cavity offers a large absorbing surface from which drugs enter the circulation rapidly. Intraperitoneal injection is a common laboratory procedure, but it is seldom employed clinically. The danger of injection and adhesions are too great to warrant the routine use of this route. However, peritoneal dialysis is sometimes a valuable procedure in the treatment of drug poisoning.

Pulmonary administration

Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route. In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled.

Topical Application

Mucous membranes. Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Occasionally, as in the application of anti-diuretic hormone to the nasal mucosa, systemic absorption is the goal.

Skin. Few drugs readily penetrate the intact skin.

Absorption of those that do is proportional to their lipid solubility since the epidermis behaves as a lipoid barrier.

4. THE BLOOD-BRAIN BARRIER

It has long been known that the bulk of the brain and the spinal cord is surrounded by a specially secreted, clear fluid called the cerebrospinal fluid (CSF). Chemical substances such as metabolites move relatively freely from the alimentary canal into the blood, but not into the CSF. As a result, the bloodlevels of sugar, amino acids, or fatty acids fluctuate over a wide range while their concentrations in the CSF remain relatively stable. The same is true for hormones, antibodies, certain electrolytes, and a variety of drugs. Injected directly into the blood, they act rapidly on peripheral tissues such as the muscles, heart, or glands, but they have little or no effect on the central nervous system (CNS).

When administered into the CSF, however, the same substances exert a prompt and strong action. The conclusion is that the substances injected into the blood do not reach the CSF and the brain with sufficient rapidity and in effective concentration.

The way in which the brain keeps its environment constant is frequently discussed in terms of a blood-brain barrier (BBB).

Once substances have found their way into the CSF, they are free to diffuse into the tissues of the brain [13]. The entry of hydrophilic and relatively large molecules into the CNS is restricted by the existence of a BBB [25]. The BBB separates the brain from the blood circulation and is involved in the homeostasis of the brain. The BBB is situated in the brain microvessels and is composed of various cell types like endothelial cells, astrocytes, microglial cells, perivascular macrophages, and pericytes. The cerebral and endothelial cells form the morphological and functional basis of the BBB.

NASAL CAVITY AND OLFACTORY SENSE

Nasal Cavity

External Nose

Terms commonly used to describe the external nose are the tip or apex, the base (which includes the nares), the root (where the nasal bones join the skull above), the dorsum

(between the root and the tip), and the bridge (the upper part of the dorsum). Only the upper third of the external nose is bony. The lower two thirds are cartilaginous.

Internal Nose

On each side of the nose are anterior and posterior openings called the nares. The posterior nares are also called the choanae. The vestibule is the anterior, skin-lined part of the nasal cavity. The nasal septum divides the nose into the two nasal fossae. The lateral wall of the nose is a complicated area anatomically. There are four nasal turbinates, or conchae. Named from below upward, they are the inferior, middle, superior, and supreme turbinates. The mucous membrane of the inferior turbinate is very rich in blood vessels and is semierectile. The several nasal meatuses are named according to the turbinates that overlie them.

Above the superior and supreme turbinates is the sphenosthmoid recess, into which the sphenois sinus opens. The inferior meatus are large blood vessels (sphenopalatine branches) under the mucosa of the lateral wall of the inferior meatus.

Both the external and the internal carotid systems provide a blood supply to the nose. The venous drainage is important because part of it, through the angular vein, leads to the inferior ophthalmic vein and eventually to the cavernous sinus. Most of the venous drainage, however, is downward through the anterior facial vein.

Lymphatic drainage of the nose is extensive and parallels the venous drainage.

The olfactory area is located high in the nasal vault above the superior turbinate. Sensory hairs extend from the surface of the olfactory area to the cells that lie deep in the mucosa.

Nerve fibres subserving the sense of smell have their cells of origin in the mucous membrane of the upper and posterior parts of the nasal cavity. The entire olfactory mucosa covers an area of about 2.5 cm. The central processes of olfactory fila are very fine unmyelinated fibres that converge to form small fascicles enwrapped by Schwann cells and pass through openings in the cribriform plate of the

ethmoid bone into the olfactory bulb. The axons of the mitral and tifted cells enter the olfactory tract, which courses along the olfactory groove of the cribriform plate to the cerebrum. Some fibres project to the medial dorsal nucleus of the thalamus and the hypothalamus. That olfactory stimuli and emotional stimuli are strongly linked is not surprising, in view of their common roots in the limbic system [26].

According to Bell [27], the olfactory system has direct neuroautonomical and neurophysiological input to the amygdala and eventually hypocampus. Therefore it is conceivable that chemical stimuli at low levels could trigger limbic dysfunction in patients who happen to meet descriptive criteria for somatization disorder It is also stated [29] that there is no blood-brain barrier in the nasal passages, limbic structure (e.g, the amygdala, olfactory bulb, and hypocampus) can become easily kindled. Therefore, olfactory nerves can transport toxins directly to the limbic system. This may result in symptoms including memory loss, irritable bowel, and migraine headaches.

It has been suggested by Shipley [28, 16], that it is possible to transport substances which come into contact with the nasal epithelium to the brain and that it is thus possible to influence the function of neurons in the brain, including some which have extensive projection to wide areas of the CNS.

6 THE OPTIC NERVE

The optic nerve, mediating vision, is distributed to the eyeball. Most of its fibres are afferent and originate in the nerve cells of the ganglionic layer of the retina. Developmentally, the optic nerves and the retinae are parts of the brain, and their fibres are provided with glia.

The optic nerve, about 4 cm long, is directed backwards and medially through the posterior part of the orbital cavity. It then runs through the optic canal into the cranial cavity and joins the optic chiasma. The optic nerve is enclosed in three sheats, which are continuous with the membranes of the brain, and are prolonged as far as the back of the eyeball. Therefore, there is a direct connection

between the optic nerve and the brain structures.

Itaya and Van Hoesen [11] described transneuronal retrograde labelling of neurons in stratum griseum superficiale of the superior colliculus following intraocular injection of wheat germ agglutinin-horseradish peroxidase. This is one of the most comprehensive reports of transneuronal transport of wheat germ agglutinin-horseradish peroxidase which studied the distribution of the conjugate in the visual system following intraocular injections in the chick, rat, and monkey [8].

7 THE ORAL CAVITY

The oral cavity is bounded anteriorly by the lips, posteriorly by the anterior faucial arc, inferiorly by the floor of the mouth and superiorly by the hard and soft palates.

The oral cavity is divided into two parts by the upper and lower alveolar process and the teeth: first, the vestibule of the mouth lying between the lip and cheek on one side and the teeth and the alveolar process on the other and second, the oral cavity proper limited externally by alveolar processes and the teeth. The tongue fills the oral cavity almost completely when the mouth is closed. The presence of a slight negative pressure in the oral cavity ensures that the tongue adheres to the hard and soft palate, thus maintaining closure of the mouth. The following parts of the tongue are distinguished; the tip, the margins, the body, the base, and the ventral surface. The tongue is covered by the mucous membrane that is continuous with the floor of the mouth. Under its anterior tip a fold of mucous membrane forms the frenum, which attaches to the floor of the mouth. Between the floor of the mouth and the tongue is the sublingual space.

The sublingual space is bounded by the mandible anteriorly and laterally; the posterior wall is formed by the styloglossus muscles, the palatoglossus muscles, and the hyoid bone. The roof is formed by the mylohyoid muscles. The epithelial lining of the oral cavity consists of the nonkeratinized stratified squamous epithelium which is

thickened in certain points such as the alveolar edges and hard palate where it is united with the underlying periosteum.

Subepithelial collection of minor salivary glands are found over the oral cavity, being more common at some parts than at others.

The normal palate at birth consists of three portions: hard palate, soft palate, and uvula. These are covered with nonciliated mucous membrane continuous with that of the alveolus and meet as a raphe (ridge) in the midline. The mucous membrane forms rugae of the oral surface of the hard palate. The soft palate is attached to the posterior margin of the soft palate. With the mouth closed the soft palate rests on the tongue, and with the mouth open it hangs free. The hard palate offers support to the floor of the nose and is covered by the dense mucosa.

Vascular supply.

The external carotid artery supplies the tongue via the lingual artery, the floor of the mouth via the sublingual artery, the cheek via the facial artery, and the palate via the ascending pharyngeal and descending palatine arteries. The latter arises from the internal maxillary artery. The venous drainage runs via the veins of the same names to the facial vein, the pterygoid venous plexus, and the internal ugular vein. There is also a connection to the cavernous sinuses via the pterygoid plexus.

The lymph drains via the regional submental, submandibular, and parotid nodes to the internal jugular chain. The lymph drainage of the base of the tongue and the floor of the mouth is to the same side and to the opposite side.

8. RECTUM

The rectum commences where the taeniae coli fuse to form a continuous longitudinal muscle coat. On account of the obliquity of the levator ani, the rectum is intimately related laterally to the pararectal space but below and laterally to the pelvic diaphragm and to the apex of the ischiorectal fossa. The pararectal space is formed by the

peritoneum above, the obturator internus and the side walls of the pelvis laterally, by the rectum medially and by the levator ani bellow.

The rectum also follows the curve of the sacral hollow in its lower two-thirds but at the level of the levator ani, where it enters the anal canal, it turns abruptly backwards and downwards.

The posterior relations of the rectum are the sacrum, the coccyx, the puborectalis muscles and the middle sacral vessels. The anterior relations differ according to sex. In males the extraperitoneal rectum is related from below upwards to the prostate, seminal vesicles, vas and bladder. In the female the infraperitoneal rectum lies immediately behind the posterior vaginal wall.

Arterial supply

The colon and rectum are supplied from the territory of the superior and inferior mesenteric arteries. The superior mesentric artery arises from the front of the aorta just below the coeliac axis. The inferior mesentric artery arises from the aorta at the under-surface of the third part of the duodenum.

The terminal portion of the inferior mesenteric artery continues down over the pelvic brim in the mesocolon as the superior haemorrhoidal artery and divides into right and left branches before subdividing into terminal anterior and posterior endarteries supplying the rectum. The middle haemorrhoidal artery supplies the middle third of the rectum. The inferior haemorrhoidal artery supplies the lower rectum. The three haemorrhoidal vessels form a comprehensive anastomosis in the submucosa of the anal canal and lower rectum.

Venous drainage

The veins of the rectum comprise the superior haemorrhoidal which drains into the inferior mesentric and portal system, and the middle and inferior haemorrhoidal which enter the systemic venous circulation via the internal iliac veins. The superior haemorrhoidal venous plexus lies in the submucosa of the upper part of the anal canal and lower 2 cm or so of the rectum. Thence five or six collecting veins

pass upwards in the wall of the rectum; at first they run in the submucosa but gradually they penetrate the muscle coat to be in the perirectal fat where they unite to form two main veins and eventually the single superior haemorrhoidal trunk. The middle haemorrhoidal vein is relatively unimportant, but the inferior haemorrhoidal vein is connected with the vertebral plexus which surrounds the spinal cords. Therfore, some compounds can come from the venous inferior haemorrhoidalus through the plexus vertebrals into the spinal fluid, and from there into the spinal cord and into the brains.

9. VAGINA

The vagina is an elastic fibromuscular canal extending upwards from the vulva at an angle of 60-70 degrees to the horizontal, although it is not straight as is generally supposed but angulated backwards. The vagina has a blind upper end except in so far that the cervix with its external os projects through its upper anterior wall.

The vault of the vagina is divided into four areas according to their relations to the cervix: the posterior fornix which is capacious, the anterior fornix which is shallow, and two lateral fornices. The posterior vagina wall is approximately 10 cm, whereas the anterior wall is approximately 8 cm, in length. The introitus is functionally closed by the labia which are in contact with each other.

If the walls are separated, the vagina of the nulliparous married woman has a diameter of approximately 4-5 cm at is lower end and is twice as wide at its upper end, but the width and length of the vagina show considerable individual variations. The functional width is determined to a large extent by the tone and contractions of surrounding muscles.

The vagina is lined by stratified squamous epithelium which also extends on to and covers the vaginal cervix as far as the external os. Normally, the surface is devoid of keratin. The epithelium is multilayered, the basal cuboidal cells being the source of a continuous production of the squamous cells above.

The epithelium does not contain glands of any kind.

The vaginal secretion consists of tissue fluids, epithelial debris, electrolytes, proteins, and lactic acid. The amount of the last is governed by the glycogen content of the epithelium and the presence of Dö derlein bacilli but, in the adult healthy vagina, is in a concentration of 0.75 per cent.

The pH varies with the level of the vagina, being highest in the upper part because of an admixture of alkaline cervical mucus. Estimates also vary according to the method used for its determination, but the generally accepted figures are from 4.0 to 5.5 with an average of 4.5. During menstruation the flow of alkaline blood raises the vaginal pH to levels of from 5.8 to 6.8.

The vagina not only "secretes"; it absorbs water, electrolytes and substances of low molecular weight. Absorption and re-absorption are believed to occur in the lateral recesses of the lower vagina.

The epithelium rests on a subepithelial connective layer which contains elastic tissue. Outside this are muscle coats in which the fibres are nearly all arranged in a crisscross spiral fashion. Outside the muscle layers is a strong sheath of connective tissue. The vaginal wall itself and the tissues around are extremely vascular so they usually bleed freely at the time of injury and operation.

In the vagina of the newborn child (by 10-14 days) the pH rises to approximately 7 and remains at that level until the approach of puberty when, with the onset of full ovarial function, the vagina assumes the features already described.

During pregnancy the amount of glycogen is increased to a maximum and the acidity of the vagina is high (pH 3.5-4.5). After the menopause the epithelium atrophies and loses its glycogen. Dö derlein's bacilli are found in fewer numbers and the pH rises to a range of 6-8. Therefore, with vaginal iontophoresis the age and the vaginal pH of the patient must be taken into account.

Vascular connection

Arterial. There are: (1) the vaginal artery mainly; (2) branches of the uterine artery; (3) branches of the internal

pudendal artery; (4) twigs from the middle and inferior rectal arteries. The vagina artery is usually a separate branch (or branches) of the internal iliac artery but may come off the first part of the uterine artery. It passes forwards and inwards low in the broad ligament to reach the lateral vaginal fornix.-

In the vaginal wall it anastomoses with the azygos branches of the circular artery of the cervix. The lower vagina is supplied from the middle and inferior rectal (haemorrhoidal) vessels and by branches from the internal pudendal artery.

Venous. A plexus of veins around the vagina connects with those around the bladder and rectum, and ultimately drains into the internal iliac veins by branches which mainly accompany corresponding arteries.

The veins of the pelvis normally accompany the arteries and have the same names. Sometimes there are two veins to one artery. There are plexuses of veins around the vagina, the urethrovesical junction and the anorectal junction and all ultimately drain into the internal iliac veins. The venous return from the rectum and pelvic colon enters the portal system by way of the inferior mesenteric veins. The pelvic plexuses and veins have communications with the presacral and lumbar channels of the vertebral plexus. This is probably the explanation for the occurrence of metastatic growths in the spine and brain when the primary tumor is in the uterus.

Each pelvic viscus drains into a venous plexus around its walls. The vestical, uterovaginal and rectal venous plexuses drain into the internal iliac veins bilaterally. On the pelvic floor the visceral venous plexuses communicate with the external vertebral venous plexus which surrounds the whole length of the vertebral column. The external vertebral plexus communicate with the internal vertebral plexus which itself receives blood from the vertebrae. Since there are very few valves in this venous system it provides a possible pathway for the spread of neoplastic disease from the pelvic viscera to the vertebrae.

In virgins, the hymen is an impediment for vaginal iontophoresis.

Hymen

The hymen is a delicate incomplete membrane guarding the entrance to the vagina prior to maturity and sexual experience. It has one or more apertures to allow the outflow of menstrual blood and, according to their number and shape, is described as being annular, crescentic, septate or cribriform. If no other way for the introduction of medication is possible and it has to be done more than once, then an incision has to be made in the hymen so that electrodes can be easily introduced into the vagina.

10. THE AUTONOMOUS NERVOUS SYSTEM

The autonomous nervous system innervates every organ in the body, creating, as Galen suggested, 'sympathy' between the various parts of the body. It has as complex a neural organization in the brain, spinal cord, and periphery as the somatic nervous system, but remains largely involuntary or automatic.

The hypothalamus can be considered the 'highest' level of integration of autonomic function [2]. It remains under the influence of the cortex and the group of structures known as the limbic system', which includes the olfactory areas, the hypocampus and amygdaloid complex, the cingulate cortex, and the septal area. The regions of the brain regulate the hypothalamus and are critical for emotional and affective expression. The hypothalamus is also concerned with maintaining homeostasis against a changing environment. The autonomic nervous system and many metabolic functions are under the control of the limbic system by means of nerve centres, many of which are situated in the hypothalamus.

The hypothalamus controls the autonomic nervous system in two ways, by means of the pituitary and hence other endocrine glands and by directed descending nervous pathways.

Lerner [14] using his electroautonomograph proved that pathology of internal organs can be initially caused by dysfunction of autonomous regulation.

11. THE LIMBIC SYSTEM

In 1878 the French neurologist and anthropologist,

Pierre Paul Broca, drew attention to a ring of tissue forming the medial wall of each cerebral hemisphere and called it the great limbic lobe, although he did not suggest a function for it. Nearly 75 years later, in 1952, Paul MacLean suggested that the components of the limbic lobe, together with the subcortical nuclei to which it is connected, are involved in the elaboration and expression of emotions, and used the term limbic system in referring to this functional circuitry. The limbic system includes the following cortical structures: the olfactory cortex, hypocampal formation, cingulate gyrus and subcallosal gyrus; as well as the following subcortical regions, which were known at that time to share direct cortical connections: the amygdala, septum, hypothalamus, epithalamus, anterior thalamic nuclei; and parts of the basal ganglia.

The limbic region of the telencephalon appears to constitute highly interconnected structures that lie between neocortical association areas on the one hand, and the hypothalamus on the other. The limbic region may thus form the gateway for neocortical cognitive influence of hypothalamic mechanism associated with motivation and emotion, and vice versa.

From the overview of the literature given above we can conclude the following.

The limbic system and the autonomous nervous system, which is in fact a united limbico-autonomic system, regulate all tissues and organs of an organism including the cardiovascular system, the gastrointestinal system, the immune systems, the brain, and others.

Many substances such as metabolic products, drugs, and other substances cannot or only to a limited extent cross the BBB from the blood into the brain. From the nasal cavity these substances can penetrate into the brain because in the area of of 2.5 cm2 of the upper posterior part of the nasal cavity, the BBB does not exist. Therefore, substances introduced into the upper part of the nasal cavity can directly enter the brain. Access to the CNS is also possible through the optic nerve and through the inferior part of the rectum.

By using the olfactory nerve and the optic nerve we are thus able to deliver compounds into the CNS, bypassing the BBB; the compounds enter thus in all parts of the CNS and of course in the CSF.

To enhance the delivery of substances into the CNS we can use the lower part of the rectum because the venae haemorrhoidales inferior is connected with the vena vertebralis around the spinal cord.

It comes therefore into the spinal fluid (CSF), and from there into the CNS. A non-invasive intravenous enhanced delivery of drugs or other biologically active compounds using the route of the sublingual space and through the vagina and upper part of the rectum is also suggested.

The above methods relate to the non-invasive delivery of biologically active compounds into the brain (CNS) or into the blood.

Iontophoresis can enhance the delivery of drugs into the organism. The present invention relates in a first embodiment to a device to enhance the delivery of an effective amount of a biologically active compound into a target organ or tissue in a living organism, comprising at least two electrodes of which at least one can function as an active electrode and one as a passive electrode, said electrodes being capable of being positioned spaced apart from one another, at preselected locations of said organism, wherein the electrodes are all connected with a selected energy source, which generates and maintains an energy field before and during the enhancement of delivery of said compound under the influence of which said compound is propelled in a direction from the active to the passive electrode and into said target organ or tissue. Due to the fact that an energy field is generated over an area which includes at least a part of the target organ or tissue, it now appeared to be possible to deliver the active compound in a direction from the active to the passive electrode.

Preferably, the present device comprises an energy source which is provided with means for internal electrical circuiting, to hold the supply of energy in rest-position, which means that it can activate the electrodes in the

compound-delivery position upon connection to said organism.

Any type of electrical current including but not limited to DC and AC of any wave form, can be used for all variants which will be described in this application.

It is observed that said preselected locations are preferably with respect to the active electrode provided with the active substance: the nostril, or the bridge on the nose for the electrode without substance, with the substance applied in the nostril separately; and a supplementary pair of active and passive electrodes applied superficially.

It is found that the electrode acting as the active electrode is provided with means for carrying the active compound in a container of some sort. Such an arrangement has the advantage that the amount of active compound to be delivered to a target organ or tissue from a preselected place at some distance of said organ or tissue can be supplied as accurate as possible. If, for example, said active electrode, provided with the active substance of choice is placed in the nostril of an animal or human being, and the passive electrode fixed on the back of the head, a generated electric field having a current intensity of up to 10 mA, will result in the almost complete penetration of the active substance into the brain.

The duration of iontophoresis is generally up to 60 minutes (sometimes up to several days).

In the present invention, the passive electrode may be split into two or more parts. It will then be possible to enhance the delivery of active substance more accurately to the desired organ or tissue, for example by said split electrode, fixed at different places of the organism, sequentially. It is in this respect observed that at least one passive electrode must preferably be fixed at the projection at the skin of said living organism, of the target organ or tissue to which the biologically active compound will be delivered.

Furthermore, it is observed that a device for the delivery of a pharmaceutical agent or drug by means of iontophoresis, is already known from US patent-5,298,017. This known device is adapted for the transmucosal and

transdermal drug delivery and to prevent short-circuiting. Nevertheless, this known device is comprised of a plurality of essentially parallel elements, including the counter electrode and the donor electrode, which are indicated in the present invention as the passive and the active electrode respectively. The problem of this known device is still that burning effects might arise, because the intensity of the current used for generating the penetration of the drug must be rather high. The device according to the invention does not give rise to such short-circuiting problems.

It is further observed that if the electrodes are not connected with the power source, preferably an electric power source, the active compound will be diffused and dispersed randomly into said organism from the location onto which said compound was applied. Only by connecting both active and passive electrodes into the circuit, the active compound will be delivered directly into the target organ or tissue.

With respect to the electrodes which can be used in the present invention, they are comprised of electrically conductive material such as a metal like aluminum, stainless steel, gold, silver, titanium, and zinc. Examples of other suitable electrically conductive materials include carbon, graphite, and metal salts like silver chloride. Electrodes may be formed of metal foil, metal screen, metal deposited or painted on a suitable carrier backing by means of calendaring, film evaporation, or by mixing the electrically conductive material in a polymer binder matrix. Alternatively, electrodes may be formed of a polymer matrix containing a conductive filler such as a metal powder, powdered graphite, carbon fibers, or other known electrically conductive filler material. Polymer based electrodes may be manufactured by mixing the conductive filler in a polymer matrix, preferably a mixture of hydrophilic and hydrophobic polymers. The hydrophobic polymers provide structural integrity, while the hydrophilic polymers may enhance ion transport. For example, metal powder, carbon powdered, carbon fibers and mixtures thereof can be mixed in a hydrophobic polymer matrix.

The energy source connected with the electrodes of the

present device is preferably a source providing an electric field, a magnetic field, high energy waves like laser beams or ultrasonic waves, etcetera., in a special embodiment. The energy source may be a combination of these sources.

In another embodiment the' energy source is a source of thermal energy. Such a source can, of course also be combined with a source as mentioned above. For example, a combination of a source of electric energy and a source of thermal energy has the advantage that a compound with a relatively high molecular weight can be delivered in the organism, because the supply of thermal energy will allow a better penetration into tissues due to dilatation effects.

In an expedient embodiment of a device according to the invention, the energy source is provided with means for changing the polarity of the electrodes connected to said energy source, in order to prevent an irritation or burning sensation in tissues at the site of electrodes. The mechanism of irritation is related to the intensity and duration of the unidirectional current of ions into tissues, as introduced by means of iontophoresis. Electrochemical burns may originate from hydrogen and hydroxide ions generated by the DC current, where H+ ions accumulate at the anode and OH- ions at the cathode, leading to pH changes at both sites. These changes cause tissue damage and eventually to electrochemical burns. This can be avoided by the periodical reversal of current polarity in order to neutralize these ions.

By temporarily changing the polarity of the electrodes, it will then become possible to overcome potential limitations in the delivery of the active compound into the target tissue. For, the changing of the polarity of the electrodes will result into a movement of the active compound in the reverse direction with respect to the initial direction.

The drug or other biologically active substance or compound can be selected from the following listed, and that are given as examples and without limitation: amino acids, anabolics, analgesics and antagonists, anesthetics, anthelmintics, anti-adrenergic agents, anti-asthmatics, anti-atherosclerotics, antibacterials, anticholesterolics,

anti-coagulants, antidepressants, antidotes, anti-emetics, anti-epileptic drugs, ant-fibrinolytics, anti-inflammatory agents, antihypertensives, antimetabolites, antimigraine agents, antimycotics, antinauseants, antineoplastics, anti-obesity agents, anti-Parkinson agents, antiprotozoals, antipsychotics, antirheumatics, antiseptics, antivertigo agents, antivirals, appetite stimulants, bacterial vaccines, bioflavonoids, calcium channel blockers, capillary stabilizing agents, coagulants, corticosteroids, detoxifying agents for cytostatic treatment, diagnostic agents (like contrast media and radioisotopes), drugs for treatment of chronic alcoholism, electrolytes, enzymes, enzyme inhibitors, ferments, ferment inhibitors, gangliosides and ganglioside derivatives, hemostatics, hormones, hormone antagonists, hypnotics, immunomodulators, immunostimulants, immunosuppressants, minerals, muscle relaxants, neuromodulators, neurotransmitters and nootropics, osmotic diuretics, parasympatholytics, para-sympathomimetics, peptides, proteins, psychostimulants, respiratory stimulants, sedatives, serumlipidreducing agents, smooth muscle relaxants, sympatholytics, sympathomimetics, vasodilators, vasoprotectives, vectors for gentherapy, viral vaccines, viruses, vitamins, and every kind of neurotropic drugs and other substances.

The invention further relates to electrodes to be used in a device according to the invention, comprising an electric conductive base member which can be connected to said selected energy source, wherein the top area of said base member is capable of supporting the biologically active compound, and all but the top area of said base member is coated with an insulating material.

The electrode should be inserted as deep as possible into the nose because of two reasons. As was mentioned before, in the upper part of the nasal cavity the BBB does not exist and can be bypassed, and secondly, the lower parts of the nasal cavity contain many capillaries and veins that provide easy access for the drugs to the bloodstream.

Such an electrode can be placed into a nostril, but can also be adapted for use in the arteries or veins or in

another body cavity or organ.

The active electrode is then inserted, for example intra-arterially or intravenously to be positioned next to a thrombus by checking with X-rays, while the passive electrode is connected outside on the body. The electric energy field then enhances the delivery of the active compound (such as an anticoagulant) completely into the thrombus, to remove the thrombus or the arteriosclerotic plaque, which may be located in the brain, in the heart or in the other organs, and thus avoid surgical interventions.

We can also use the iontophoresis to deliver drugs directly into tumours or other morphological disorders in the stomach, in the urinary tract, in the bladder, intraperitoneally, intrathoracally, etc. In this case, we insert the active electrode into one of these organs or cavities, and by means of this active electrode we deliver the active compound directly into the morphological disorder; the passive-electrode must be fixed superficially on the body. In this way we enhance the delivery of the beneficial compound into the morphological disorder.

Preferably, the base member of the present electrode has a substantial frusto-conical hollow shape. Such a shape allows the easy insertion into a nostril; nevertheless, any other shape might do as well, such as a tube-like shape.

In an expedient embodiment, such an electrode according to the invention contains at least one hole or opening in the area coated with the insulating material present in the base member. Such an opening will prevent a complete blocking of the organ flow in which said electrode has been inserted, for example a nostril. In this way, it will be possible to continue normal breathing through the nose during the procedure.

According to an expedient embodiment, the electrode according to the invention is provided with a container for the active compound to be delivered, having a security-stop connection with the top area of the electrode. In this way it is possible deliver a biologically active compound to a certain tissue or organ discontinuously without the necessity of removal and re-insertion of the present device.

The container can be made of any suitable material or combination of materials, that fulfills relevant criteria with respect relevant criteria with respect to compatibility with the drug or other substance or compound of interest and with the biological environment, but also with respect to ease of manufacturing, sterilizability, re-usability, low environmental impact, flexibility, connectibility, disposability and durability. Furthermore, the drug container or reservoir should be constructed of any material in such way that it is adapted to absorb and hold a sufficient quantity of liquid in order to permit transport of drug through its wall by means of iontophoresis. Optionally, the container should hold a self-sealing membrane or valve that allows the in-situ refilling with drug solution, without the necessity of removal and re-insertion of the present device.

For example sponges, gauzes or pads consisting of cotton or other absorbent fabric, either or natural or synthetic origin, may be used. More preferably, containers or reservoirs are composed, at least in part, of one or more hydrophylic polymers. Typical preference is for hydrophylic polymers because water is the preferred ion transport medium and hydrophylic polymers have a relatively high equilibrium water content. Multilayered solid polymer container matrices are composed, at least in part of hydrophylic polymer. Insoluble hydrophylic polymer matrices are preferred over soluble hydrophylic polymers since the probability of delivering insoluble polymer by iontophoresis is very low.

The container matrix can be cross-linked with the drug components in place such as a silastic matrix, or the polymers can be prefabricated and sorbed with the components from solutions, for example with sponges or pads made of cellulose or woven fibre. The container may also consist of a gel matrix structure, or be of a classical reservoir type holding a liquid.

The polymers can be either of linear or cross-linked type.

Examples of suitable hydrophylic polymers include polyethylene glycols, polyacrylates, polyoxyethylene alkylethers, polyvidone, poloxamers, polyethylene oxides,

polyvinyl alcohols, polyacrylamide, hydroxyethylcellulose, hydroxypropylcelluiose, hydroxypropylmethyl-cellulose, co-polyesters, cyclodextrins, crospovidone, crosslinked dextrans, crosscarmellose sodium, natural gums, and starch, and mixtures thereof. Optionally, the container matrix may contain a hydrophobic polymer, to improve structural integrity. Preferably the hydrophobic polymer is heat fusible in order to enhance the lamination of container layers.

Examples of suitable hydrophobic polymers include but are not limited to polyethylene, polypropylene, ethylene-vinylacetate copolymers, polyvinylacetate, polyisobutylenes, polyamides, polyurethanes, polyvinylchloride, and acrylic or methacrylic resins.

The container may be a polymeric matrix structure formed by mixing the selected drug, solvent, electrolyte, or other component(s) with an inert polymer by means of melt blending, solvent casting, compression or extrusion.

The form of the container may be such as to enable its combination and attachment or coupling with the active electrode. The form, size and shape of the active electrode and its drug container are determined by the physiological environment related to its application and introduction into the body, for instance in the nostril, in the blood vessels, in the stomach, in the rectum, and in the vagina.

The connection of the container onto the active electrode may be of permanent or semi-permanent type, or of cartridge type for easy exchange of containers. Use of suitable adhesives for permanent connection of container and active electrode is foreseen, while physical locking and connecting means like slide lock, luer-lock, screw lock are more suitable for semi-permanent connections to enable exchange or cartridge type containers.

The energy source providing an electric field is preferably adapted to provide a current of up to 25 mA. Such a current appeared to be sufficient in practical tests. Nevertheless, it will be obvious for the expert that some deviation of this value might be used as well, and will also fall within the scope of the present invention.

The invention is also directed to an enhanced delivery

of an effective amount of a drug into an internal target organ or tissue of an organism, such as a mammal, particularly a human being, being in need of such a delivery with such a drug, wherein the delivery of said compound is enhanced as such into said organ or tissue from a carrying location in the body of said organism by means of energy-stimulated penetration generated and maintained by a field between at least two electrodes that may be split, upon connection with a selected energy source, of which electrodes one can function as an active electrode and one as passive electrode, of which at least one electrode is placed on the outer layer of said organism, and one electrode, having the opposite polarity, is placed near place where said active compound is applied.

It is in this respect observed that the passive electrode must be fixed at a place on the skin of the organism, which is the projection of the target tissue to be treated with the biologically active compound, for example when the active compound is administered directly to the CNS via the nose, the active electrode is placed in the nose, while the passive electrode is placed on the back of the head. To obtain the desired effects, the passive electrode is wetted with water or hydrogel or an electricity conducting adhesive before its fixation to the skin, whereas the active electrode is provided with the active compound before its fixation. It is nevertheless also possible to use a hydrogel or conductive adhesive onto the container of the active compound, for example in order to temporarily allow fixation onto the outside of a tumor.

For example a patient with a tumour in the right temporal lobe. In this case the active electrode with the drug is inserted in the nasal cavity and of the split passive electrode one part is fixed on the back of the head and the other part is fixed on the right temporal region on the projection of the tumour. Then the drug is delivered into the brain and the concentration will be much higher in the region of the tumour. Preferably the location of the active electrode holding the drug container is spaced apart from the target tissue by a membrane or tissue having low resistance.

A direct penetration, for example from the nasal cavity into the brain, is thus possible due to the absence of the blood-brain barrier.

According to the invention, it now also appeared to be possible to enhance the delivery of the biologically active compound from it's carrying location in the body to said target organ or tissue, without any substantial distribution into surrounding parts of the organism, for example the bloodstream.

According to a preferred embodiment, the delivery of said active compound is enhanced transnasally to the CNS from the nostril by passing the BBB by using a current intensity of up to 10 mA between an active electrode introduced into at least one nostril, and a passive electrode fixed on the back of the head or another place of the head.

According to a variant of this embodiment the delivery of said compound is enhanced transnasally to the CNS by using an active electrode fixed externally on the nose of the organism, a passive electrode fixed on the back of the head or another place, while the active compound is applied intranasally after the generation of the energy field.

Expediently, the active electrode is split into two parts, one of which is fixed externally to the nose, and the other one, being provided with the said active compound is introduced into a nostril.

According to a further variant of the invention, the delivery of said compound is enhanced into some specific region of the brains by using an active electrode fixed intranasally or extranasally and a split passive electrode, whereof one part is fixed externally on the projection of said specific region on the head, and another part is fixed on the back of the head or another place of the head, while said compound has been applied into a nostril.

A variant thereof comprises that the passive electrode is split into two parts, of which one is connected with the back of the head, and the other part is connected with the forehead or another region of the head of said organism, while the active electrode carrying the active compound is connected with the palate in the mouth of said organism.

For the delivery of the active compound in a certain hemisphere or part of a hemisphere it is necessary to fix the active electrode into one nostril and to fix the split passive electrode on the mastoideus, or another place of the body, and on the projection of the tumor.

It is observed that an embodiment comprises a kit consisting of two different sets of active and passive electrodes, wherein one set consisting of an active electrode to be placed into a nostril and being provided with a biologically active substance, and a passive electrode to be fixed on the back of the head; and another set consisting of an active electrode, wetted in water, to be fixed at the part of the head opposite to the place of treatment, and a passive electrode wetted in water to be fixed on the projection of the place of treatment, wherein both sets of electrodes can be connected to two different sources, if desired, or to one source, will also fall within the claimed scope of protection of the present invention.

It is further observed that the present type of iontophoresis (i.e. according to the invention) can be combined with other methods which are suited for the delivery of biologically active compounds. Exemplary for such methods are diathermy, use of magnetic field, use of ultrasonic energy, high energy like laser etc., or use of compounds providing a dilatation effect. These dilatating compounds can either be administered separately via oral or parenteral routes or be combined with the drug delivered via iontophoresis. Diathermy and dilatators are preferred when the delivery of biologically active compounds having a high molecular weight must be enhanced through some tissue of the body, for example by passing the BBB.

According to a variant embodiment of the process according to the invention, the compound is enhanced transocular to the CNS from the eyelid by using a current intensity of up to 10 mA between an active electrode fixed over the active compound carried by said eyelid, and a passive electrode fixed on the back of the head or on the mastoides of the organism.

According to another variant embodiment of the process

according to the invention the compound is delivered to the CNS by using an active electrode, brought into contact with said compound, and both being introduced into the lower part rectum of the organism, and a passive electrode, fixed on the spine or another place, by using a current intensity of up to 10 mA.

According to another variant embodiment of the present invention, the active electrode being provided with the biologically active compound is placed in the sublingualis space, and the passive electrode is fixed sub-mandibularly to enhance the delivery of said compound intravenously.

According to another variant embodiment of the present invention, the active electrode being provided with the biologically active compound is placed in the rectum or vagina, and the passive electrode is fixed externally on the spine or another place on the skin of the organism to enhance the delivery of said compound intravenously.

According to another variant embodiment of the present invention, the active electrode being provided with the biologically active compound is introduced into a vein or artery, and the passive electrode is fixed on the projection on the skin of the pathological organ or tissue, for instance a thrombus, to which a antocoagulant or fibrinolytic agent is delivered in a high concentration. This can avoid a systemic effect like hemorrhage in the inner organs.

According to another variant embodiment of the present invention, the active electrode being provided with the biologically active compound is placed in the stomach or bladder or intraperitoneally, and the passive electrode is fixed externally on the skin of the organism to enhance the delivery of said compound into the tumour or lesion.

The present invention is further explained in the following practical embodiments.

a) We suggest realization of iontophoresis according to a first embodiment, through the nasal cavity. We called this method intracerebral transnasalis. Our method has the following advantage. The mucous membrane of the nasal cavity has a low electrical resistance. Therefore, according to Ohms law the current intensity by the same voltage is much more

higher than the iontophoresis applied through the skin. It is known that the quantity of substance introduced by current is directly proportional to the current intensity. Hereby, the proportion of the substance introduced into an organism (into the brain) will be higher than if it were done through the skin. The concentration of the substance in the blood introduced by our method will be low or absent. Thus side effects caused by entrance of the substance into the systemic circulation will be minimal, in contrast to intravenous and oral administration.

We suggest the following method for this embodiment.

Two electrodes (metal, conductive rubber or another conductive material, such as mentioned before) must be introduced into the nostrils. The electrodes have to be covered by the cotton or other material wetted in the solution of the necessary drug or compound and to touch the nose mucous membrane. Electrodes must be introduced as deep as possible, but without causing unpleasant feelings. Electrodes themselves must touch neither skin nor the nose mucous membrane, only through the container with active substance.

Another electrode or split electrode covered by cotton or other material and wetted in the water has to be fixed on the mastoid processes or to be fixed on the back of the head in the area of cervical vertebrae or another place. Depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 10 mA. Subsequently the current intensity can be decreased until any unpleasant feeling disappears.

b) We suggest realization of iontophoresis according to a second embodiment through the oral cavity. We called this method intracerebral transoral. The nasal cavity and the pharynx are connected with each other and all together are called nasopharynx. The oral cavity is connected to the nasal cavity by the upper part of the pharynx. Moreover, the upper part of the oral cavity, that is the hard and soft palates, is a bottom of the nasal cavity. The hard palate is a thin bone structure and as well as the soft palate is covered from both sides by the epithelium, which is known to have low

resistance and to conduct easily the current.

We suggest the following method for this embodiment. An electrode (metal, conductive rubber or another conductive material) must be introduced into the mouth and brought into contact with the hard palate. During the procedure the mouth must be tightly shut and the tongue must cling tightly to the hard palate and to the electrode in order to keep it on its place. Therefore, the electrode does not need any additional fixation, since its position on the hard palate remains unchanged. The electrode has to be covered by the cotton or other material wetted in the solution of the necessary drug or substance and to cling close to the hard palate. The electrode must be introduced as deep as possible, but without causing unpleasant feelings. The electrode itself must touch neither skin nor the mucous membrane of the oral cavity, only through the container (here the cotton wool or other kind of pad) with active substance. Another split electrode covered by cotton or other material and wetted in water has to be fixed on the mastoid processes or a single passive electrode has to be fixed on the back of the head in the area of cervical vertebrae or at any other place on the head. Depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 10 mA or more. Subsequently the current intensity can be decreased until unpleasant feelings disappear.

The duration of the iontophoresis is up to 60 minutes or more, sometimes several days, dependent on the dosage of a necessary substance, its concentration, the resistance of the epithelium on the hard palate, and other factors. Influenced by the current, a drug or other substance penetrates into the nasal cavity and from there through the olfactory structures into the CNS, without having to pass the BBB.

c) We suggest realization of iontophoresis according to the third embodiment through the eyeballs. We called this method intracerebral transocularis. Our method has the following advantage.

The skin of the eyelid has a resistance lower than that on the rest of the skin surface and a resistance of the

cornea and of the sclera is negligible.

We suggest the following method for this embodiment.

A split active electrode (metal, conductive rubber, or another conductive material) must be placed over the eyes. The active electrodes have to be covered by the cotton or other material wetted in the solution of the necessary active substance and to touch the skin. Electrodes themselves must not touch the skin, but only through the container (here the cotton) holding the active substance. Another split electrode covered by cotton or other material and wetted in the water has to be fixed on the mastoid processors or on another place or a single passive electrode has to be fixed on the back of the head in the area of cervical vertebrae or on another place. Depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 10 mA. Subsequently the current intensity can be decreased until unpleasant feelings disappear. This method is called transocular.

Variations of this method called transcorneal and transscleral are realized by applying two special electrodes directly to the cornea and the sclera, respectively. The electrodes brought in the contact with the cornea or the sclera must deliver the necessary drug or active substance. Another split electrode covered by cotton or other material and wetted in water has to be fixed on the mastoid processes or one part of the passive electrode has to be fixed on the back of the head in the area of cervical vertebrae on another place, and another part has to be fixed on the forehead. Depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 2 mA or more.

d) We suggest realization of iontophoresis according to a fourth embodiment through the sublingual space of the oral cavity. We called this method "Non-invasive intravenous delivery of drugs and other substances". Our method has the following advantage. The oral cavity and its part the sublingual space is covered by epithelium, which is known to have low resistance and to conduct easily the current.

We suggest the following method for this embodiment.

An electrode (metal, conductive rubber, or another conductive material) has to be covered by the cotton or other material wetted in the solution of necessary active compound and must be introduced into the mouth and brought into the contact with the mucosa of the sublingual space. During the procedure the mouth must be tightly shut in order to keep the electrode on its place. Therefore, the electrode does not need any additional fixation, since its position in the sublingual space remains unchanged. The electrode has to be covered by the cotton or other material wetted in the solution of the necessary drug or substance. The electrode itself must touch neither skin nor the mucous membrane of the oral cavity, only through the container with active substance.

Another electrode covered by cotton or other material and wetted in the water has to be fixed on the skin of the submandibular region. Depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 5 mA or more.

The duration of this kind of iontophoresis is up to 60 minutes or more, dependent on the dosage of a necessary drug, its concentration, etc.

e) We suggest realization of iontophoresis through the rectum or the vagina. We called this method "Non-invasive intravenous transrectal delivery" and "Non-invasive intravenous transvaginal delivery" of drugs or other substances", respectively. Our method has the following advantage. The rectum and the vagina are covered with the epithelium, which is known to have low resistance and to conduct easily the electric current. According to Ohms law the current intensity by the same voltage has to be much more higher than the iontophoresis done through the skin. It is known that the quantity of substance introduced by the current is directly proportional to the current intensity. Hereby, the proportion of the substance introduced into the organism will be higher than if it were done through the skin. In the blood, the concentration of the substance introduced by our method will be the same as by intravenous administration. We suggest the following method for this

embodiment.

An electrode (metal, conductive rubber, or another conductive material) has to be covered by the cotton or other material wetted in the solution of necessary active compound and must be introduced into the rectum or the vagina and brought into contact with the mucosa of the space. During the procedure the rectum must be free from the excrements (faeces). The electrode does not need any additional fixation, its position in the rectum or in the vagina remains unchanged. Another electrode covered by cotton or other material and wetted in water has to be fixed on the skin of the sacralis or superpubitalis or on another place. Depending on individual tolerance (pressure or some other unpleasant feelings), current intensity can increase up to 5 mA or more.

The duration of this kind of iontophoresis is up to 60 minutes or more, dependent on the dosage of a necessary drug, its concentration, etc.

It is observed that the above mentioned embodiments must not be interpreted as being limitative. Other embodiments which are obvious for the expert upon reading the description and claims will fall within the scope of the present invention.

The invention will be explained further in the following examples and the accompanying drawings wherein

- figure 1 shows a particular embodiment of an electrode according to the invention, whereas
- figures 2 to 6 show graphically the results obtained by using a device and method according to the invention, while - figures 7a and 7b show the conveyance route of an active substance from a nostril into the brains.

In figure 1, the electrode comprising the conductive base member is represented by 1; this base member has preferably a hollow form, and is expediently coated with an insulating material for example a plastic, except the top areas, which carries the biologically active substance 2. The base member 1 is further connected to a source of current by means of line 3, connected to the conductive base material. The base member is further provided with one or more

perforations 4. Although the electrode as represented in the figure has a tube-like form, a substantial frusto-conical form or another form can be used. Further, the perforations 5 can have any form.

In figure 7a and 7b the delivery of an active compound into the brains is schematically shown.

More specifically the compound is according to fig. 7a applied into a nostril by means of the active electrode a. The passive electrode b is fixed on the back of the head. Both electrodes are connected with an energy source I. Upon activation of the electrodes a and b the active compound will be forced in a direction from a to b, as indicated by dotted lines f. To enhance the delivery of active compound into the target tissue e, for example to a tumour, the direction of delivery of the active substance can be bended by means of another pair of electrodes, i.e. the active electrode c and the passive electrode d. These electrodes c and d are connected to a different energy source II.

It is nevertheless possible, according to a special embodiment, as shown in fig. 7b, to use a split passive electrode, consisting of passive electrode b1 and passive electrode b2, both being connected with energy source 1. Also in this case, the direction of delivery of the active substance from the nostril into the brains has been given by dotted lines f.

EXAMPLE 1

We conducted the transnasal iontophoresis in 60 patients and in 20 healthy volunteers in the age from 20 to 40. Forty five of 60 patients suffered from vegetative distonia with sleep disorders, 40 of which showed significant improvement, 4 have showed no improvement, and the rest have showed some improvement. These patients were administered the antidepressant amitryptilin. The other 15 of 60 patients suffered from migraine headaches. These patients were administered Papaverine hydrochloride. Twelve of them have showed significant improvement and 3 showed no improvement.

Iontophoresis sessions were conducted daily for 15-30 minutes, with a total of 20-25 sessions. As a rule, the

improvement came after 3-5 sessions. To healthy volunteers we administered a solution of piracetam. 16 of them have shown significant improvement of memorizing abilities and increase of activity.

Another experiment was conducted in 5 male volunteers in the age from 20 to 30. We investigated penetrability of benzylpenicillin introduced transnasally into the cerebrospinal fluid (CSF) and into the blood.

At he beginning we carried out an endolumbal puncture with each subject, taking 1 ml of the CSF. The needle was left in place of the puncture for the duration of the experiment (1,5 - 2 hours). Then we took 1 ml of blood from the arm vein. Both fluids were subsequently investigated for the presence of benzylpenicillin by means of a microbiological assay. This analysis was conducted as follows. We took three Petri dishes with the Streptococcus culture. The first dish remained only with the streptococcus culture. To the second one was added one drop of the CSF. To the third one was added one drop of blood from the vein. All three dishes were subsequently placed into a thermostat to analyze the ability of the CSF and the blood to destroy the streptococcus. Then we wetted cotton covers in the benzylpenicillin solution (0,2 g [200 000 units] per 5 ml of distilled water). A split electrode covered by these cotton covers was introduced deeply into both nostrils. Another split electrode covered by cotton wetted in water was fixed on the mastoid processes. The intensity of galvanic current by the iontophoresis was 2.0 mA.

The duration of the procedure was 30 minutes. In 1.5 hour after the iontophoresis with benzylpenicillin again 1 ml of the CSF and 1 ml of the blood were taken. Following the same procedure described above we investigated them for the presence of benzylpenicillin. We found out that after 1.5 hour of iontophoresis, the CSF showed significant presence of benzylpenicillin . However, no benzylpenicillin could be demonstrated in the blood since no lysis of the streptococcus occurred. This was a direct evidence that the iontophoresis allowed benzylpenicillin to penetrate into the brain tissue without entering the blood.

EXAMPLE 2

An experiment with the transocular method was conducted in 5 male volunteers in the age from 20 to 30. We investigated the penetration of benzylpenicillin introduced transocular into the cerebrospinal fluid (CSF) and into the blood. At he beginning we carried out an endolumbal puncture with each subject, taking 1 ml of the CSF. The needle was left in place of the puncture for the duration of the experiment (1,5 - 2 hours). Then we took 1 ml of blood from the arm vein. Both fluids were subsequently investigated for the presence of benzylpenicillin by means of a microbiological assay. This analysis was conducted as follows. We took three Petri dishes with the Streptococcus culture. The first dish remained only with the streptococcus culture. To the second one was added one drop of the CSF. To the third one was added one drop of blood from the vein. All three dishes were subsequently placed into a thermostat to analyze the ability of the CSF and the blood to destroy the streptococcus.

Then we wetted cotton covers in the benzylpenicillin solution (0,2 g [200 000 units] per 5 ml of distilled water). A split electrode covered by these cotton covers was placed over each of the the eyes. Another split electrode covered by cotton wetted in water was fixed on the mastoid processes. The intensity of galvanic current by iontophoresis was 0. 8 - 2 mA. The duration of the procedure was 30 minutes. In 1.5 hour after iontophoresis with benzylpenicillin we took again 1 ml of CSF and 1 ml of blood. Following the same procedure described above we investigated them for the presence of benzylpenicillin. We found out that after 1.5 hour of iontophoresis, the CSF showed significant presence of benzylpenicillin. However, no benzylpenicillin could be demonstrated in the blood since no lysis of the streptococcus occurred. This was a direct evidence that the iontophoresis allowed the benzylpenicillin to penetrate into the brain tissue without entering the blood.

Electric current does not have a negative impact on the brain and is even used for treatment of a series of the nervous system disorders. This treatment is called cerebral

electrostimulation or electrosleep. This method is realized by application of electrodes bilaterally placed over the eyes and the mastoid or neck region [9].

One of the most comprehensive overviews of the transocular iontophoresis has been given by Sarraf and Lee [21].

EXAMPLE 3

Methylprednisolone hemisuccinate was according to the invention administered to rabbits, using the following protocols.

Materials and Methods

HPLC assay for Methylprednisolone hemisuccinate and methylprednisolone: The mobile phase was a mixture of acetonitrile and phosphate buffer pH6 (30:70% v/v). The flow rate was 1.2 ml min^{-1}. The effluent was monitored at 242 nm. Injection volume 2 μ l. Retention times: Methylprednisolone hemisuccinate (MPS) 6.5 min and Methylprednisolone (MP) 14.6 min. Limits of quantitation 10 ng/ml for both compounds. Intra and interday coefficients of variation were < 5%. CASno. MPS 2375-03-3; MP 83-43-2. Molecular weight: MPS 496.50; MP 374.50. Gross formula: MPS C26H33NaO8.

1000 mg Methylprednisolone hemisuccinate sodium (Solumedrol® , batch 12/2000A 95LI3 CLI02, Upjohn, the Netherlands) was dissolved in 5 ml distilled water (200 mg/ml).

Animals

New Zealand White rabbits (2.5-3 kg body weight) were obtained from the Central Animal Laboratory (University of Nijmegen, The Netherlands). The animals were anesthetized with 0.5 ml/kg Hypnorm (fentanylcitrate 0.315 mg/L and fluanisone 10 mg/ml; Janssen Pharmaceutica, Tilburg, the Netherlands). The animals were intubated and mechanically ventilated with N20, 02, 1:2 (v/v), and ethrane 2.4%. Endtidal C02 was maintained at 4%. The artery femoralis was cannulated with a Venflon 2, 18 G catheter.

Mechanical ventilation was maintained with an Amsterdam Infant Ventilator MK2 (Hoek Loos, Amsterdam, the Netherlands) and a Capnomac (Datex, Hoevelaken, the Netherlands). At the

end of the experiment the animals were killed by the arterial injection of 2 ml pentobarbital 60 mg/ml (Narcovet® , Apharmo, Arnhem, the Netherlands)

Iontophoresis:

A stimulator was used. The applied current was 3 mA, at 8000 Hz, pulse duration 119 μ sec, puls interval 6 μ sec. Remark: this type of current was used because it is less irritating at the nerve ending and is therefore less painful. Electrodes, encapsulated in cotton wool and saturated with drug solution were firmly placed in the nasal passage, the opposite electrode was placed with a wet sponge pad at the shaven back of the head (clear skin). The nose electrodes were used in the positive (+) and negative (-) mode in separate experiments.

Sampling

Blood samples (2 ml) of each animal were collected in heparinized polypropylene tubes just before the start of the iontophoresis (t=0) and at 15, 30, 45 and 60 min after the start of the stimulation. A spinal fluid sample of 1 ml was collected from the animal after killing and just before the brain was dissected. After killing of the animal the whole brain was dissected. The right Temporal lobe, the Frontal lobe, Brain stem and remaining were collected.

Sample preparation

During the whole experiment (6 h), blood samples were kept at room temperature (20 degrees C). Thereafter the blood samples were centrifuged at 3000 g, and plasma was stored in duplo at -20 degrees C until analysis. Brain and liquor were stored at -20 degrees C until analysis.

Drug analysis

The HLPC system consisted of a Marathon autosampler (Separations, Hendrik Ido Ambacht, the Netherlands), a Spectra Systems P 4000 quaternary gradient pump, a Spectra Systems UV 1000 detector (Thermoseparations, Breda, the Netherlands) and a Hitachi D2500 integrator (Merck, Amsterdam, the Netherlands). The column was a Spherisorb 50DS (250 x 4.6 mm) with a guard column (15 x 4.6 mm) packed with 5μ m C18 reversed phase material (Chrompack, Bergen op Zoom, the Netherlands).

Sample preparation

150 gl plasma was vortexed for 10 sec with 150 μ l acetonitrile. The mixture was centrifuged at 3000 g for 5 min. 20 μ l of the clear supernatant was injected onto the column.

Braintissue. Two ml of distilled water was added to 1 gram of brain tissue. The mixture was homogenized in an ultratorax apparatus (Ystral, Dottingen, Germany) at 10,000 rpm during 30 seconds. The homogenate was centrifuged at 3000 g during 5 min and further treated like plasma.

Rabbit I

Two cotton wools, saturated with MPS 200 mg/ml were placed for one hour in the nostrils.

Rabbit 2

Two cotton wools plus electrodes saturated with MPS 200 mg/ml were placed for one hour in the nostrils. Stimulation with +3mA.

Rabbit 3

Two cotton wools plus electrodes saturated with MPS 200 mg/ml were placed for one hour in the nostrils. Stimulation with -3mA.

Rabbit 4

5 mg/kg (12.5 mg) MPS was given intravenously in 5 min. Blood samples were taken at 0, 1, 3, 5, 10, 15, 20, 25, 30, 40, 50 and 60 min. Brain samples were taken.

Rabbit 5

1 mg/kg (2.5 mg) MPS was given intravenously in 5 min. Blood samples were taken at 0, 1, 3, 5, 10, 15, 20, 25, 30, 40, 50 and 60 min. Brain samples were taken.

Rabbit 7

Two cotton wools plus electrodes saturated with MPS 0. 5 ml 200 mg/ml (dose 100 mg; the electrodes were dipped in 1 ml solution) were placed for one hour in the nostrils. Stimulation with -3mA. Fourth experiment. More solvent used, and electrodes firmly placed deep in the nasal cavity. The following results were obtained.

TABLE 1

Plasma concentrations (μ g/ml) of methylprednisolone

hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after installation of a MPS saturated cotton wool in the nostrils of each rabbit and without and with positive and negative iontophoresis.

Time	Rabbit number					
(min)	1		2 (+3mA, 1h.)		3 (-3mA, 1h.)	
	MPS	MP	MPS	MP	MPS	MP
0	0	0	0	0	0	0
15	0.19	0.12	0.01	0.12	0.54	0.15
30	0.23	0.12	0	0.11	0.22	0.11
45	0.16	0.16	0	0.17	0	0.02
60	0.21	0.20	0	0.13	0	0.01

(+) means : positive electrode into the nostril;
(-) means : negative electrode into the nostril.

The values obtained with rabbit Nr. 2 compared with those obtained with rabbit Nr. 3 show that a positive electrode into the nostril is the wrong polarity, whereas the negative electrode into the nostril is the right polarity for this kind of substance.

It is further observed that the plasma concentration of 0.15 μ g/ml for rabbit Nr. 3 (-), obtained after 15 min was due to the fact that only after about 5 min the effect of the electrical current is seen. In fact, the negative current was given 5 minutes after installation of a MPS saturated cotton wool in the nostrils.

The concentrations of both substances in the brains were also measured. The following results were obtained for the concentrations of the compounds in the brains.

TABLE 2

Brain concentrations (μ g/g) of methylprednisolone hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after installation of a MPS saturated cotton wool in the nostrils of each rabbit and without and with positive and negative iontophoresis.

Tissue	Rabbit number					
	1		2 (+3mA, 1h.)		3 (-3mA, 1h.)	
	MPS	MP	MPS	MP	MPS	MP
Frontal Lobe	0	0	1.02	0	0	1.20
Temporal Lobe right	0	0	0	0	0	0.52
Brain stem	0	0	0	0	0	3.73
Brain remains	0	0	0	0	0	0.70

Fig. 2 shows the results obtained with rabbit Nr. 1 graphically.

Fig. 3 shows the result obtained with rabbit Nr. 3 graphically.

TABLE 3: Plasma concentrations (μ g/ml) of methylprednisolone hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after installation of a MPS saturated cotton wool in the nostrils of each rabbit and negative ionophoresis

Time (min)	Rabbit number 6	
	MPS (-1mA, 1h.)	MP
0	0	0
15	0.0	0.0
30	0.0	0.0
45	0.0	0.0
60	0.0	0.0
Spinal fluid	0	0

TABLE 4: Brain concentrations (μ g/g) of methylprednisolone hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after installation of a MPS cotton wool in the nostrils of each rabbit and negative iontophoresis.

Tissue	Rabbit number 6	
	MPS (-1mA, 1h.)	MP
Right Frontal Lobe	0	0
Left Frontal Lobe	0	0.16
Right Temporal Lobe	0	0.09
Left Temporal Lobe	0	0
Cerebellum	0	0
Brain stem	0	0
Brain rest	0	0
Cervicalis spinal cord	0	0
Toracilis spinal cord	0	0
Lumbalis spinal cord	0	0

From the results of the tables 3 and 4 appears that a current intensity of 1 mA is probably too small to effect an acceptable transport of the drug to all parts of the brains. Results are graphically given in fig. 4

TABLE 5: Plasma concentrations (μ g/ml) of methylprednisolone hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after installation of a MPS saturated cotton wool in the nostrils of each rabbit and negative iontophoresis

Time (min)	Rabbit number Nr. 7	
	MPS (-3mA, 1h.)	MP
0	0	0
15	0.0	0.0
30	0.98	0.78
45	0.40	0.97
60	0.25	1.00
Spinal liquid	0.30	1.16**

TABLE 6: Brain concentrations (μ g/g) of methylprednisolone hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after installation of MPS saturated cotton

wool in the nostrils and negative iontophoresis

Tissue	Rabbit number 6	
	MPS (-1mA, 1h.)	MP
Right Frontal Lobe	0	0.95
Left Frontal Lobe	0	1.84
Right Temporal Lobe	0	2.27
Left Temporal Lobe	0	0.36
Cerebellum	0	0.69
Brain stem	0	0.41
Brain rest	0	1.71
Cervicalis spinal cord	--	--
Toracalis spinal cord	0	0.10
Lumbalis spinal cord	--	--

The results of the tables 5 and 6 are graphically given in fig. 5.

COMPARATIVE EXAMPLE

To show the superior results of the application of a biologically active substance according to the invention, compared with the application by-means of an intravenous injection, the plasma concentrations and the brain concentrations were measured in rabbits, which were treated in both ways. The following results were obtained.

TABLE 7: Plasma concentrations (μ g/ml) of methylprednisolone hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after intravenous injection of MPS 1 mg/kg and 5 mg/kg, respectively.

Time (min)	Rabbit number (dose) 4 (5 mg/kg)		5 (1 mg/kg)	
	MPS	MP	MPS	MP
0	0	0	0	0
1	72.91	12.11	8.79	1.17
2.5	55.19	13.18	1.77	0.32
5	14.12	7.98	0.46	0.30
10	3.47	5.75	0.22	0.28
15	1.48	3.97	0.14	0.25
20	1.13	3.13	0.18	0.24
25	0.87	2.95	0.11	0.23
30	0.67	2.64	0.10	0.19
40	0.42	2.00	<0.1	0.16
50	0.28	1.62		0.17
60	0.19	1.38		0.16

TABLE 8: Brain concentrations (μ g/ml) of methylprednisolone hemisuccinate (MPS) and methylprednisolone (MP) in a rabbit after intravenous injection of MPS 1 mg/kg and 5 mg/kg, respectively

Tissue	Rabbit number (dose) 4 (5 mg/kg)		5 (1 mg/kg)	
	MPS	MP	MPS	MP
Right Frontal Lobe	0	0	0	0
Left Frontal Lobe	0	0	0	0
Right Temporal Lobe	0.0	0.069	0	0
Left Temporal Lobe	0.0	0.060	0	0
Cerebellum	0.0	0.055	0	0
Brain stem	0	0.038	0	0
Brain rest	0	0.090	0	0
Cervicalis -	0	0.092	0	0
Toracalis - spinal cord	0	0.076	0	0
Lumbalis -	0	0.076	0	0

The results obtained with rabbit Nr. 4 are graphically given in fig. 6.

Remark: If we compare a normal human intravenous dose of methylprednisolone hemisuccinate of 1 mg/kg, this cannot be detected in the brain. If we give a very high dose of 5 mg/kg intravenously, only methylprednisolon can be detected in the brain in a very low concentration.

Contrary, if we deliver methylprednisolone hemisuccinate intranasally to the brain by means of iontophoresis as described before, the concentration of methylprednisolone in the brain is between 10 and 100 times higher.

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DEFINITIONS AND TERMINOLOGY:

1. Biologically active compounds: This invention is useful in the delivery of directly or indirectly active substances or compounds or drugs within their broadest sense, or any other substance or compound of interest, in order to achieve a therapeutic, diagnostic or other desired, usually beneficial, effect.

Biologically active compounds, agents or substances may relate to compounds of chemical, biological

or biotechnological origin; examples include organic and inorganic chemical substances, and compounds pertaining to animal, human, microbiological, plant, or viral origin.

Throughout this text the terms compound(s), drug(s) and substance(s) are used interchangeably.

2. Blood brain barrier: The barrier separating the blood from the parenchyma of the central nervous system. Presumably it consists of the walls of the cappilaries of the central nervous system and the surrounding glial membranes (glial end-feet). Abbreviation used: BBB

3. Cerebrospinal fluid: Abbreviation used: CSF

4. Container: any receptacle or reservoir that holds a liquid compound or a compound dissolved in a solvent or combination of these.

Alternatively, the container material may form part of the matrix hat holds the biologically active compound.

CLAIMS

1. A device to enhance the delivery of a drug or other substance or compound of interest into a selected target organ or tissue of an organism, comprising a special apparatus, special electrodes, one of the special electrodes carrying a special container with the selected drug or other substance or compound of interest, said electrodes being capable of being positioned at preselected locations of said organ or tissue, wherein the electrodes are all connected with a selected energy source which generates and maintains an energy field before and during the enhanced delivery of said substance or compound, under the influence of which delivery is accomplished in a direction from the active to the passive electrode and into said organ or tissue.

2. A device according to the claim 1, wherein said device comprises an energy source which is provided with means for internal electrical circuiting the supply of energy in rest position of the device, which will automatically activate the electrodes in the delivery position upon connection to said organism.

3. A device according to claim 1 or 2, wherein said active electrode is provided with means for carrying said drug or other biologically active substance or compound.

4. A device according to one or more of the claims 1 to 3, wherein said active and/or said passive electrode are split into two or more parts.

5. A device according to the claims 1 or 2, wherein said energy source is selected from the group comprising sources providing an electric field, a magnetic field, ultrasonic waves, high energy waves like laser beams, or a combination thereof.

6. A device according to the claims 1 or 2, wherein said energy source is a source of thermal energy or a combination of such a source with another source of energy.

7. A device according to claim 4, wherein said energy source providing an electric field is adapted to provide a current of up to 25 mA, preferably up to 10 mA.

8. An assembly comprising a device as defined in

one or more of the claims 1 to 7, wherein the active electrode is provided with at least one drug, or other biologically active substance or compound of interest.

9. An electrode to be used in a device according to claim 1; comprising an electric conductive base member which can be connected to said selected energy source, wherein the top area of said base member is capable of supporting the drug or other biologically active substance or compound, and all but the top area of said base member is coated with an insulating material.

10. An electrode according to claim 9, wherein said electrode is provided with a container for the drug or other biologically active substance or compound to be delivered into a targer organ or tissue, having a closable connection with the top area of the electrode.

11. An electrode according to the claims 9 or 10, wherein said base member has a substantial frusto-conical hollow or other form.

12. An electrode according to one or more of the claims 9 to 11, wherein at least one through-opening is present in the area coated with the insulating material in said base member.

13. Use of a drug or other biologically active substance or compound of interest for the manufacture of an iontophoretic assembly comprising of an electrode as defined in one or more of the claims 9 to 11, and said compound, wherein said compound is for delivery directly or by carrier and is selected from the group of drugs and other substances or compounds of interest, that can be selected from the following listed, and that are given as examples and without limitation:

amino acids, anabolics, analgesics and antagonists, anesthetics, anthelmintics, anti-adrenergic agents, anti-asthmatics, anti-atherosclerotics, antibacterials, anticholesterolics, anti-coagulants, antidepressants, antidotes, anti-emetics, anti-epileptic drugs, ant-fibrinolytics, anti-inflammatory agents, antihypertensives, antimetabolites, antimigraine agents, antimycotics, antinauseants, antineoplastics, anti-obesity

agents, anti-Parkinson agents, antiprotozoals, antipsychotics, antirheumatics, antiseptics, antivertigo agents, antivirals, appetite stimulants, bacterial vaccines, bioflavonoids, calcium channel blockers, capillary stabilizing agents, coagulants, corticosteroids, detoxifying agents for cytostatic treatment, diagnostic agents (like contrast media and radioisotopes), drugs for treatment of chronic alcoholism, electrolytes, enzymes, enzyme inhibitors, ferments, ferment inhibitors, gangliosides and ganglioside derivatives, hemostatics, hormones, hormone antagonists, hypnotics, immunomodulators, immunostimulants, immunosuppressants, minerals, muscle relaxants, neuromodulators, neurotransmitters and nootropics, osmotic diuretics, parasympatholytics, para-sympathomimetics, peptides, proteins, psychostimulants, respiratory stimulants, sedatives, serumlipidreducing agents, smooth muscle relaxants, sympatholytics, sympathomimetics, vasodilators, vasoprotectives, vectors for gentherapy, viral vaccines, viruses, vitamins, and every kind of neurotropic drugs and other substances.

14. Use of an electrode, provided with a drug or other substance or compound of interest, in the manufacture of an iontophoretic device, for the enhanced delivery of said substance or compound to a target organ or tissue of said organism without obtaining significant plasma levels of said drug, substance or compound by generating and maintaining an electric field over said target organ or tissue before and during the delivery of said drug or other substance or compound of interest.

15. Use according to claim 14, wherein said electrode is an electrode as defined in one or more of the claims 9 to 12.

16. An enhanced delivery of an effective amount of a drug or other biologically active substance or compound into an internal target organ or tissue of an organism, such as a mammal, particularly a human being, being in need of such a delivery with such a drug, or other substance or compound of interest, wherein said compound is enhanced as

such to said organ or tissue from a carrying location in the body of said organism by means of energy-stimulated penetration generated and maintained by a field set between at least two electrodes being split or not, upon connection with a selected energy source, of which electrodes one electrode can function as an active electrode and one as passive electrode, of which at least one electrode is placed on the skin layer of said organism, and one electrode, having the opposite polarity, is placed near the place where said drug or other substance or compound of interest is to be delivered.

17. An enhanced delivery according to claim 15, wherein said carrying location is spaced apart from the target organ or tissue by a membrane having a low electric resistance.

18. An enhanced delivery according to claims 15 or 16, wherein said drug or other substance or compound of interest is delivered transnasally into the central nervous system from the nasal cavity bypassing the blood brain barrier, by using a current intensity of up to 10 mA or more, between an active electrode introduced internally into at least one nostril, and a passive electrode fixed on the head.

19. An enhancement according to claims 15 or 16, wherein the delivery of said drug or other substance or compound of interest is enhanced transnasally to the central nervous system by using an active electrode fixed externally on the nose of the organism, a passive electrode fixed on the head, while the active compound is applied intranasally after the generation of the energy field.

20. An enhanced delivery according to one or more of the claims 16 to 18, wherein the active electrode is split into two parts, one of which is fixed externally to the nose, and the other one, being provided with the said active compound is introduced into a nostril.

21. An enhanced delivery according to one or more of the claims 16 to 18, wherein the delivery of said drug or other substance or compound of interest is enhanced into some specific region of the brain by using an active

electrode fixed intranasally or extranasally and a split passive electrode, whereof one part is fixed externally on the projection of said specific region on the head, while said compound has been applied into a nostril.

22. An enhanced delivery according to one or more of the claims 16 to 18, wherein the delivery of said drug or other substance or compound of interest is enhanced into some specific region of the brain, for example to a tumour, the direction of delivery of the active substance can be bended by means of another set of active and passive electrodes, connected to a different energy source.

The first pair of electrodes being positioned in the nasal cavity and on the back of the head, while the second pair of electrodes is positioned as follows: the passive on the projection of the tumour on the outside of the skull and the active, this time wetted in water, on the opposite side of the head, relative to the last mentioned passive electrode.

23. An enhanced delivery according to any of the claims 16 and 17, wherein the passive electrode is split into two parts, of which one is connected with the back of the head, and the other part is connected with the forehead of said organism, while the active electrode carrying the drug or other substance or compound of interest is connected with the palate of the mouth of said organism.

24. An enhanced delivery according to any of the claims 16 and 17, wherein said drug or other substance or compound of interest is delivered transocular to the central nervous system from the eyelid by using a current intensity of up to 10 mA between an active electrode fixed over the drug or other substance or compound of interest carried by said eyelid, and a passive electrode fixed on the back of the head of the organism.

25. An enhanced delivery according to any of the claims 16 and 17, wherein said drug or other substance or compound of interest is delivered to the central nervous system by using an active electrode, brought into contact with said compound, and both being introduced into the lower part of the rectum of the organism, and a passive

electrode, fixed on the spine or other place, by using a current intensity of up to 10 mA.

26. An enhanced delivery to claim 16, wherein the active electrode being provided with the drug or other substance or compound of interest is placed in the sublingual space, and the passive electrode is fixed submandibulary or in another place, to deliver said drug or other substance or compound of interest intravenously.

27. An enhanced delivery according to claim 16, wherein the active electrode being provided with the drug or other substance or compound of interest is placed in the rectum or vagina, and the passive electrode is fixed externally on the spine or another place on the skin of the organism to deliver said drug or other substance or compound of interest intravenously.

28. An enhanced delivery according to claim 16, wherein said active electrode being provided with the drug or other substance or compound of interest is introduced into a vein or artery, and brought directly to the pathological point, for instance a thrombus, and the passive electrode is fixed on the projection on the skin of the pathological organ or tissue to which said drug or other substance or compound of interest is delivered.

29. An enhanced delivery according to claim 16, wherein said active electrode being provided with the drug or other substance or compound of interest is introduced into the stomach or bladder or intraperitoneally or into another cavity or tissue, and the passive electrode is fixed externally on the skin of the organism to enhance the delivery of said compound into the tumour or lesion.

30. The container holding the drug or other substance or compound of interest to be connected to the active electrode according to Claim 14, can be made of any suitable material or combination of materials, that fulfills relevant criteria with respect to compatibility with the drug or other substance or compound of interest and with the biological environment, but also with respect to ease of manufacturing, sterilizability, re-usability, low environmental impact, flexibility, connectibility,

durability and disposability.

31. The drug container or reservoir to be connected to the active electrode according to Claim 14, should be constructed of any material in such way that it is adapted to absorb and hold a sufficient quantity of liquid in order to permit transport of drug through its wall by means of iontophoresis.

32. Optionally, the drug container or reservoir to be connected to the active electrode according to Claim 14, should hold a self-sealing membrane or valve that allows the in-situ refilling with drug solution, without the necessity of removal and re-insertion of the present device.

33. The drug container or reservoir to be connected to the active electrode according to Claim 14, could consist for example of sponges, gauzes or pads consisting of cotton or other absorbent fabric, either or natural or synthetic origin, may be used. More preferably, containers or reservoirs are composed, at least in part, of one or more hydrophylic polymers.

34 The drug container or reservoir to be connected to the active electrode according to Claim 14, may consist of a multilayered solid polymer matrices, composed, at least in part, of hydrophylic polymer. Insoluble hydrophylic polymer matrices are preferred over soluble hydrophylic polymers since the probability of delivering insoluble polymer by iontophoresis is very low.

35. The drug container or reservoir to be connected to the active electrode according to Claim 14, may consist of a matrix that can be cross-linked with the drug components in place such as a silastic matrix, or the polymers can be prefabricated and sorbed with the components from solutions, for example with sponges or pads made of cellulose or woven fibre. The container may also consist of a gel matrix structure, or be of a classical reservoir type holding a liquid. The polymers can be either of linear or cross-linked type. Examples of suitable hydrophylic polymers include polyethylene glycols, polyacrylates, polyoxyethylene alkylethers, polyvidone,

poloxamers, polyethylene oxides, polyvinyl alcohols, polyacrylamide, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl-cellulose, co-polyesters, cyclodextrins, crospovidone, crosslinked dextrans, crosscarmellose sodium, natural gums, and starch, and mixtures thereof.

36. The drug container or reservoir to be connected to the active electrode according to Claim 14, may consist optionally of a matrix containing also a hydrophobic polymer, to improve structural integrity. Preferably the hydrophobic polymer is heat fusible in order to enhance the lamination of container layers. Examples of suitable hydrophobic polymers include but are not limited to polyethylene, polypropylene, ethylene-vinylacetate copolymers, polyvinylacetate, polyisobutylenes, polyamides, polyurethanes, polyvinylchloride, and acrylic or methacrylic resins.

37. The drug container or reservoir to be connected to the active electrode according to Claim 14, may be a polymeric matrix structure formed by mixing the selected drug, solvent, electrolyte, or other component(s) with an inert polymer by means of melt blending, solvent casting, compression or extrusion.

38. The drug container or reservoir to be connected to the active electrode according to Claim 14, may have such a form as to enable its combination and attachment or coupling with the active electrode. The form, size and shape of the active electrode and its drug container are determined by the physiological environment related to its application and introduction into the body, for instance in the nostril, in the blood vessels, in the stomach, in the rectum, and in the vagina.

39. The drug container or reservoir to be connected to the active electrode according to Claim 14, may have a connection of permanent or semi-permanent type, or of cartridge type for easy exchange of containers. Use of suitable adhesives for permanent connection of container and active electrode is foreseen, while physical locking and connecting means like slide lock, luer-lock, screw lock

are more suitable for semi-permanent connections to enable exchange or cartridge type containers.

40. The drug or other biologically active substance or compound of interest according to claim 13, intended for enhanced delivery by means of an iontophoretic assembly comprising of an electrode as defined in one or more of the claims 9 to 11 and contained in a container or reservoir as defined in the claims 28 to 35, should be in part ionized, which can be brought about by dissolution in a medium or solvent that is able to conduct electric current and posesses an electric dipole, preferably a polar solvent having a high dielectric constant, allowing the separation of oppositely charged ions. Examples of some useful polar solvents include but are not limited to Water, Glycerin, Ethylene glycol, Methyl alcohol, Ethyl alcohol, n-propyl alcohol, and mixtures thereof. The degree of dissolution and subsequent ionization can be improved and regulated by means of the addition of suitable electrolytes forming buffer systems in the selected polar solvent or mixtures thereof.

41. With respect to the electrodes which can be used in the present invention according to claims 1 to 4, and 8 to 15, they are comprised of electrically conductive material such as a metal like aluminum, stainless steel, gold, silver, titanium, and zinc. Examples of other suitable electrically conductive materials include carbon, graphite, and metal salts like silver chloride. Electrodes may be formed of metal foil, metal screen, metal deposited or painted on a suitable carrier backing by means of calendaring, film evaporation, or by mixing the electrically conductive material in a polymer binder matrix. Alternatively, electrodes may be formed of a polymer matrix containing a conductive filler such as a metal powder, powdered graphite, carbon fibers, or other known electrically conductive filler material.

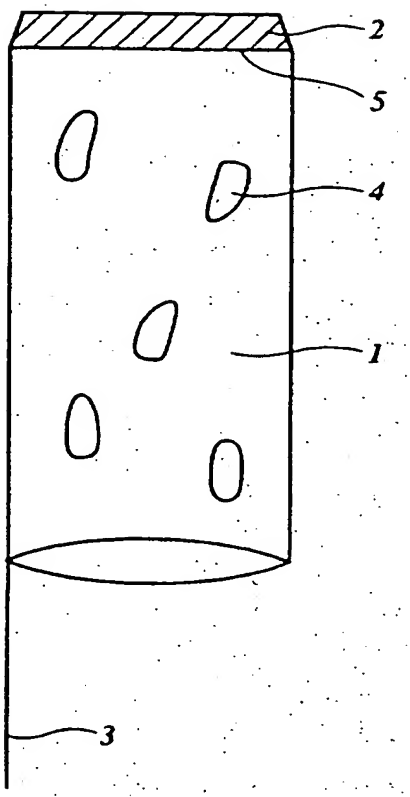

Fig. 1

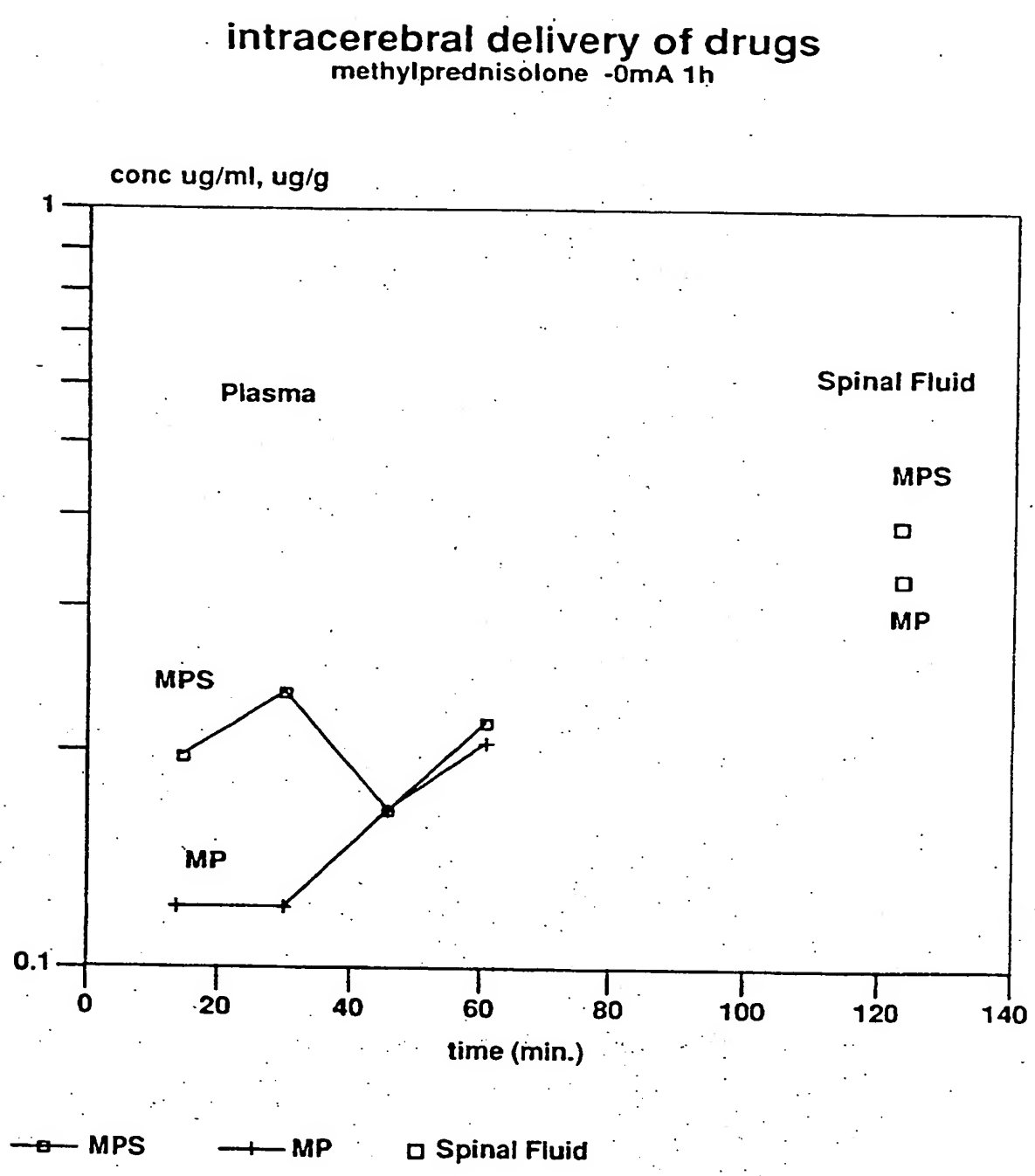
intracerebral delivery of drugs
methylprednisolone -0mA 1h
conc ug/ml, ug/g
1
0.1
Plasma
Spinal Fluid
MPS
MP
MPS
MP
0
20
40
60
80
100
120
140
time (min.)
MPS
MP
Spinal Fluid

Fig. 2

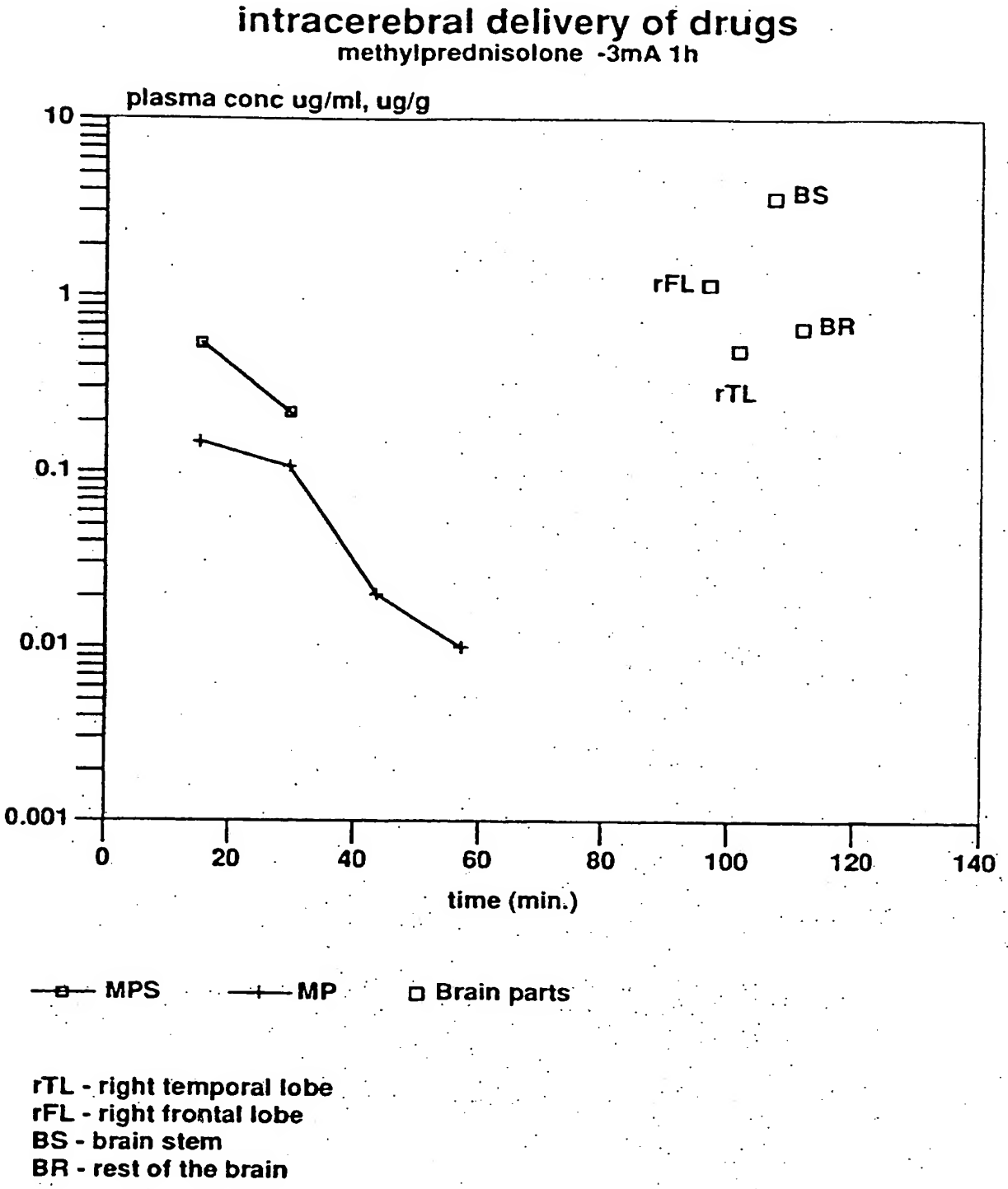

Fig. 3

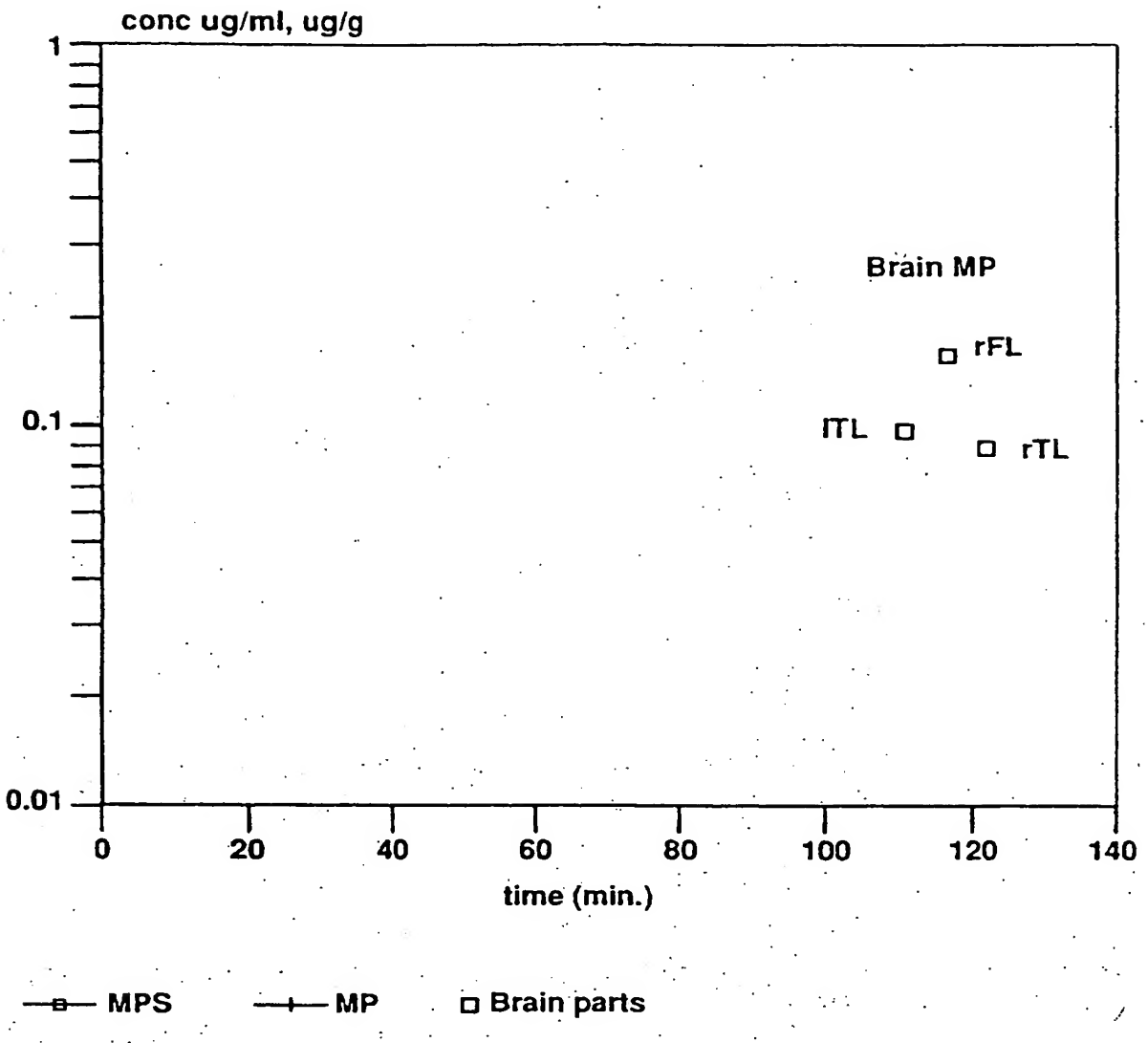
intracerebral delivery of drugs
methylprednisolone -1mA 1h
conc ug/ml, ug/g
1
0.1
0.01
Brain MP
rFL
lTL
rTL
0
20
40
60
80
100
120
140
time (min.)
MPS
MP
Brain parts

Fig. 4

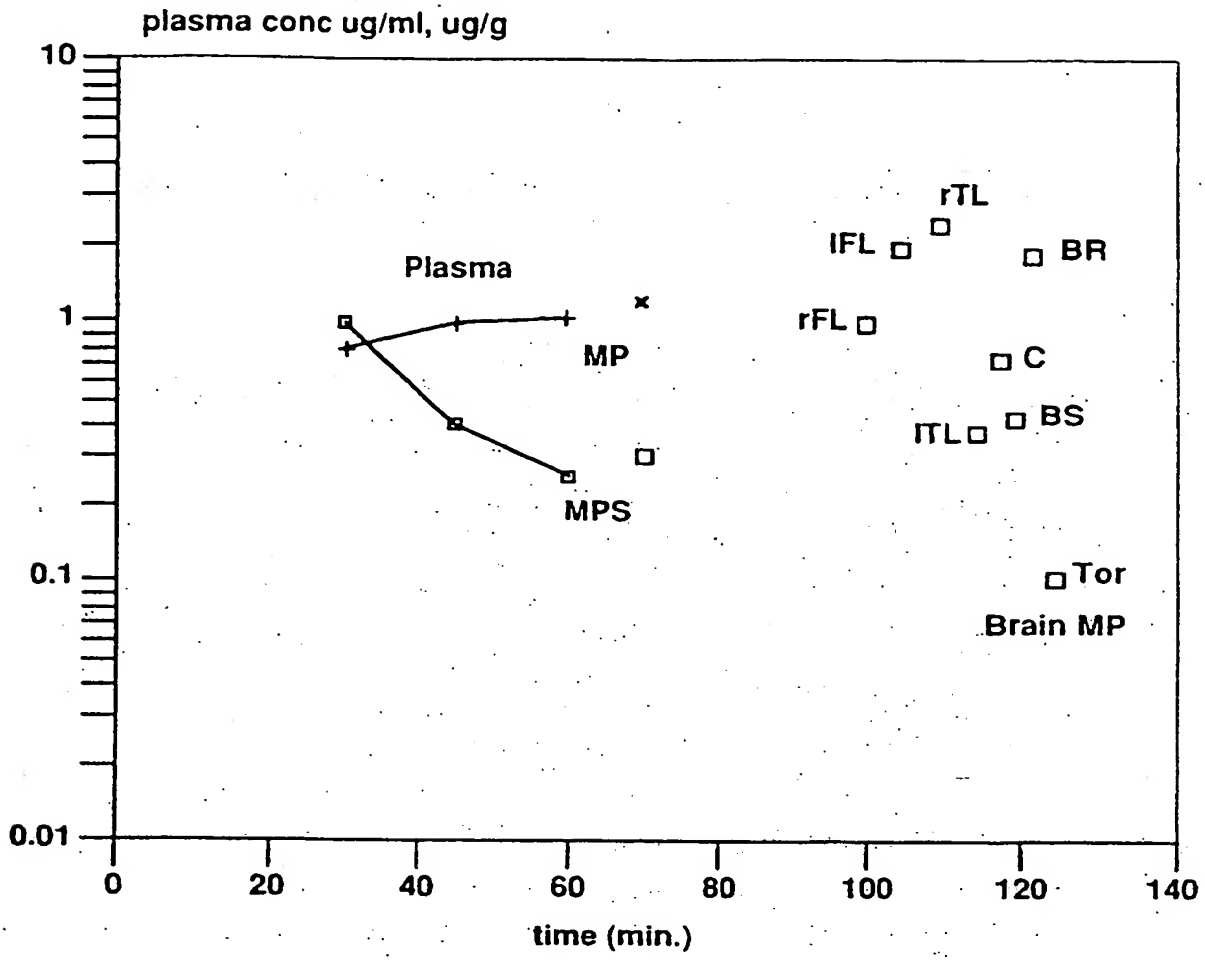
intracerebral delivery of drugs
methylprednisolone -3mA 1h
plasma conc ug/ml, ug/g
10
1
0.1
0.01
0
20
40
60
80
100
120
140
time (min.)
Plasma
MP
MPS
rTL
lFL
BR
rFL
C
lTL
BS
Tor
Brain MP
MPS
MP
Brain parts
Spinal Fluid
Spinal Fluid
lTL - left temporal lobe
FTL - right temporal lobe
lFL - left frontal lobe
rFL - right frontal lobe
BS - brain stem
C - cerebellem
BR - rest of the brain
Tor - spinal cord (part toracicus)

Fig. 5

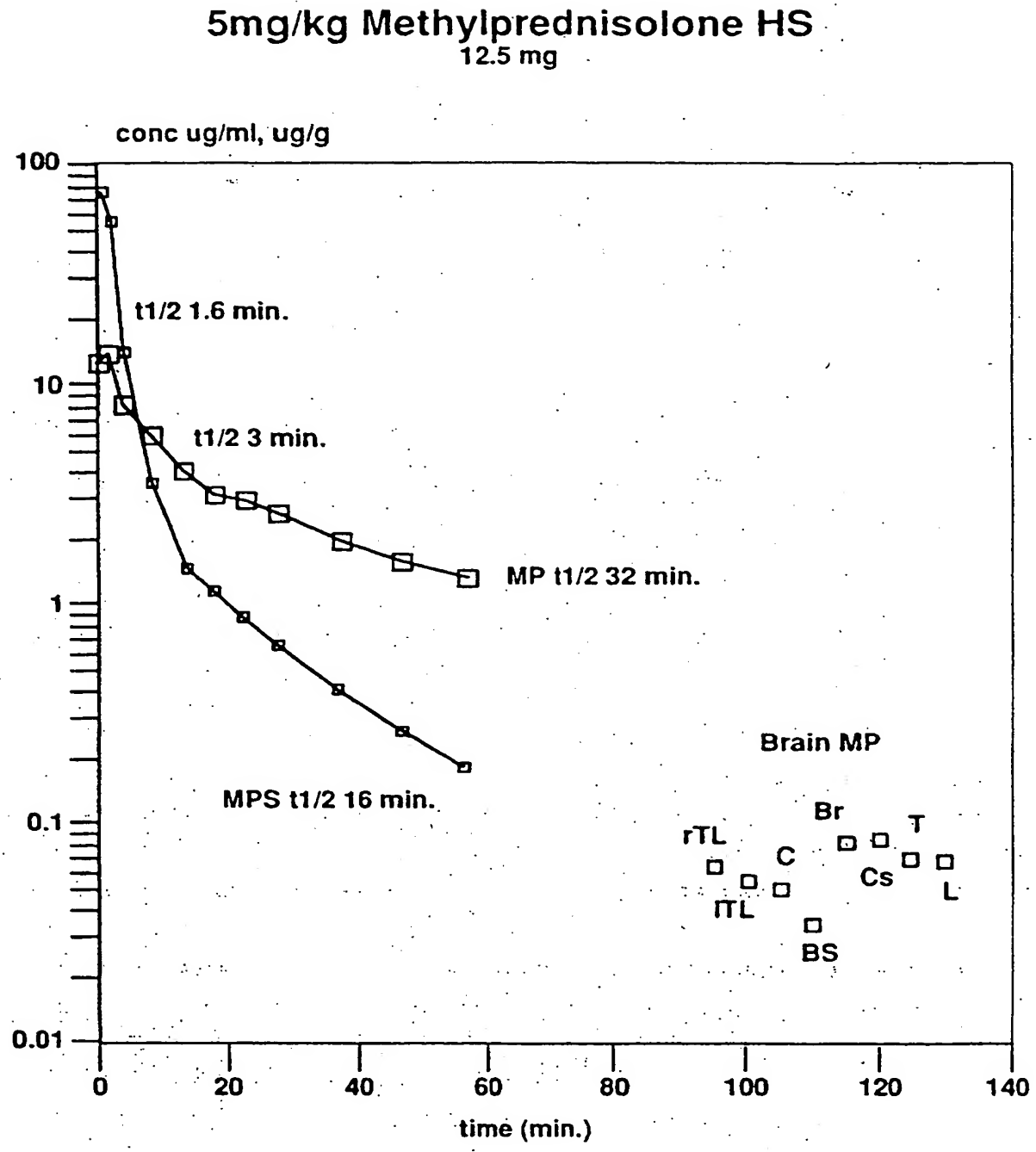
5mg/kg Methylprednisolone HS
12.5 mg
conc ug/ml, ug/g
100
10
1
0.1
0.01
t1/2 1.6 min.
t1/2 3 min.
MP t1/2 32 min.
MPS t1/2 16 min.
Brain MP
Br
T
rTL
C
Cs
L
lTL
BS
0
20
40
60
80
100
120
140
time (min.)

Fig. 6

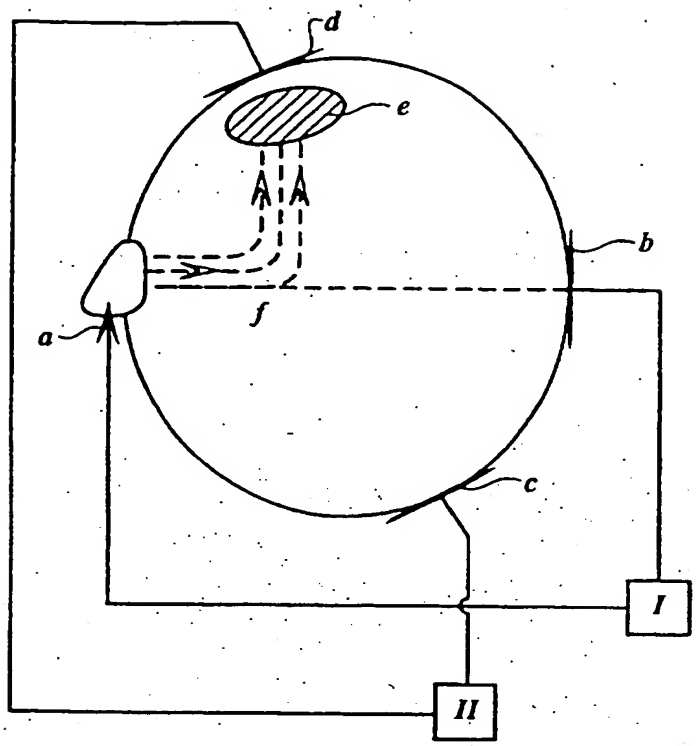

Fig. 7a

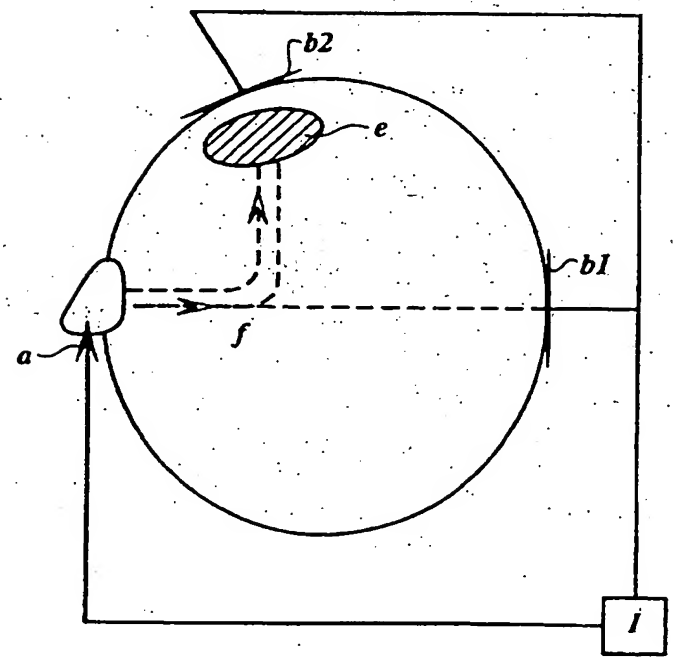

Fig. 7b

INTERNATIONAL SEARCH REPORT

Inten. nal Application No
PCT/EP 96/05086

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 298 017 A (THEEUWES FELIX ET AL) 29 March 1994 cited in the application	1-3,5,8, 9,13-17, 30,31, 33-38, 40,41
Y A	see the whole document	18-23 24-27

X	US 3 831 598 A (TICE I) 27 August 1974	1-3,5,8, 13,14, 16,30, 31,33, 38,39
A	see the whole document	23,26

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 1997	28.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Ferrigno, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 96/05086

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 122 137 A (G. ERLANGER) 25 February 1964	1-3,5,8, 13,14, 16,30
A	see the whole document	24
X	US 5 169 384 A (BOSNIAK STEPHEN L ET AL) 8 December 1992 see the whole document	1,4,16
Y		18-23
X	WO 94 05361 A (CORTRAK MEDICAL INC) 17 March 1994 see the whole document	1,3,5,6, 9,13-16, 28,30, 34,38
X	EP 0 498 353 A (BECTON DICKINSON CO) 12 August 1992 see the whole document	1,2,5, 8-10, 13-15, 30,40,41
X	FR 328 311 A (J.J. STANGER) 6 June 1903 see the whole document	1,10,11
X	WO 91 16945 A (FEIRING ANDREW JONATHAN) 14 November 1991 see abstract	1
X	EP 0 378 132 A (TOMAS JUSTRIBO JOSE RAMON) 18 July 1990 see the whole document	1
A	DATABASE WPI Section Ch, Week 8416 Derwent Publications Ltd., London, GB; Class B07, AN 84-098813 XP002004807 see abstract & SU 992 075 A (LVOV TUBERCULOSIS) 30 January 1983 see figures	16,21
A	EP 0 470 338 A (EMPI INC) 12 February 1992 see the whole document	32

1

INTERNATIONAL SEARCH REPORT

:rnational application No.
PCT/EP 96/05086

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 13-41
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
SEE ANNEX

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO SUPPLEMENTAL SHEET B

The application does not meet the requirements of Article 6, Rule 6.1 (a) and 6.3 PCT. Consequently there is an uncertainty about the real subject-matter for which the protection is sought and is not obvious what is the intended contribution to the prior art.

In particular claims 13 to 15 and 30 to 41 are very broad and contain vague statements or suggestions; furthermore most of them "suggest" many alternative within the same claim. The alternative are such that it is impractical any attempt to separate them in differing subject-matters. Furthermore many of them appear to be known features.

Claims 16 to 29 are ambiguous, since it is not clear whether or not they define a "method". If claims 16 to 29 were to be interpreted as "method of delivery", they would form a subject-matter under Article 17(2) (a) (i) PCT, i.e. excluded from the Search under Rule 39.1 (iv) PCT.

Because of the above ambiguities the Search has been carried out for 13 to 41 in so far as possible and reasonable, in accordance with Rule 33.3 PCT.

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